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PRIMARY DOUBLE CANCER *

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Writers on pathologic subjects speak indiscriminately of primary multiple tumors and primary multiple cancers. These two conditions should, however, be differentiated. The incidence of multiple tumors originating from different germinal layers, whether benign or malignant, is apparently of casual interest only, whereas that of multiple cancers, as will be shown later, is significant from a doctrinal point of view also.

Primary double or multiple cancer is a malignant condition in which a person is affected with two or more cancers which have started spontaneously and independently either in different organs or in different structures in the same organ. According to Billroth,[1] two cancers found in the same organism may be considered as being independent growths only (1) when they vary in structure; (2) when each tumor can be traced to its respective matrix, and (3), when metastases can be traced to the respective mother tumor. These requirements can, however, rarely be fulfilled. In the first place, two tumors originating in the same system of tissues, as in different parts of the intestines, may not vary in structure; in the second place, it is oftentimes impossible to trace the point of departure of a tumor in an advanced stage of its growth and finally, the third postulate can be complied with only when each respective tumor gives metastases of its own.

Owing, apparently, to diagnostic difficulties, cases of primary multiple cancer are only rarely recognized in pathologic laboratories. In a recent study, Siebke [2] found in the literature only 53 reports of undeniable cases of primary multiple cancers to which he added 2 cases of his own. According to his statistics, about 1 case is found in every thousand necropsies. In 1902, von Hansemann [3] noted that from

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1. Billroth, quoted by Borst, M.: Allgemeine Pathologie der malignen Geschwülste, Leipzig, Hirzel, 1924.

2. Siebke, N.: Ueber multiple Carcinome, Ztschr. f. Krebsforsch. **23**: 66, 1926.

3. Von Hansemann: Die microscopische Diagnose der bösartigen Geschwülste, Berlin, 1902; Die gleichzeitige Vorkomen verscheidenartiger Geschwülste bei derselben Person, Ztschr. f. Krebsforsch. **1**:183, 1904.

0.3 to 0.5 per cent of all cancers are primarily multiple. Puhr [4] found only 6 double cancers in the same person in 6,718 necropsies performed in the Pathologic Institute at Budapest. These figures, however, must be accepted with reservation. In reality, the incidence of this disease is probably higher than that recorded. Nevertheless, it must be admitted that cases are an uncommon occurrence.

Three patients with primary double cancer have come to my attention. The clinical and pathologic reports follow:

REPORT OF CASES

CASE 1.—*A married man, aged 70, with the complaint of excruciating epigastric pain. Death. Necropsy disclosing a primary carcinoma of the tail and body of the pancreas with metastases to lungs and liver; also a primary carcinoma of the prostate.*

History.[5]—The patient, whose past and family histories were unimportant, complained of severe excruciating pain in the epigastrium, cough and progressive weakness. His illness dated back a little more than a year, at which time he noticed that he was getting weaker and also that he was losing weight. Two or three months later a sharp pain in the epigastrium occurred, which gradually increased in intensity and frequency.

Physical examination, except for cachexia and evidences of considerable loss of weight, gave negative results. The laboratory tests also gave negative results. While under observation, the patient developed a persistent diarrhea with tenesmus which grew worse daily. The frequent attacks of sharp epigastric pain already described persisted up to the patient's death. He died in an advanced stage of cachexia with emaciation.

Nepropsy.—Pancreas: A large tumor mass was found occupying the entire tail of the pancreas and also a large part of the body (fig. 1). The rest of the pancreas appeared normal. The tumor weighed 300 Gm. and measured 6 by 9 by 7 cm., being almost as hard as a stone. The surface was irregular, as if it were composed of innumerable small nodules enclosed within a thin, translucent capsule. On cut surface it had a mosaic appearance, being composed of numerous lobules separated by thin strands of fibrous tissue; in gross, the architecture and color of the tumor roughly approached that of the normal pancreas.

The duodenal orifice of the duct of Wirsung was patent, and a probe could pass for about 5 cm. in the duct. The remote part of the duct was obliterated. The tumor compressed the celiac axis and solar plexus and overlay the anterior surface of the aorta without leading, however, to any vascular constriction.

Histologically, the tumor (fig. 2) was made up of polygonal epithelial cells, the size of a large lymphocyte. The cellular cytoplasm was abundant and was finely granular; the vesicular nucleus was large, and was provided with an eccentrically situated, irregularly round nucleolus. Individual cells were separated from one another by a narrow clear space.

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4. Puhr, L.: Ueber die Multiplizität der Geschwülste, Ztschr. f. Krebsforsch. **24**:38, 1927.

5. A detailed clinical history of this case was given by the author previously in a report: Some Clinical Aspects of Primary Carcinoma of the Pancreas, Boston M. & S. J. **196**:640 (April 21) 1927.

Fig. 1 (case 1).—Primary double cancer; carcinoma of the tail and body of the pancreas.

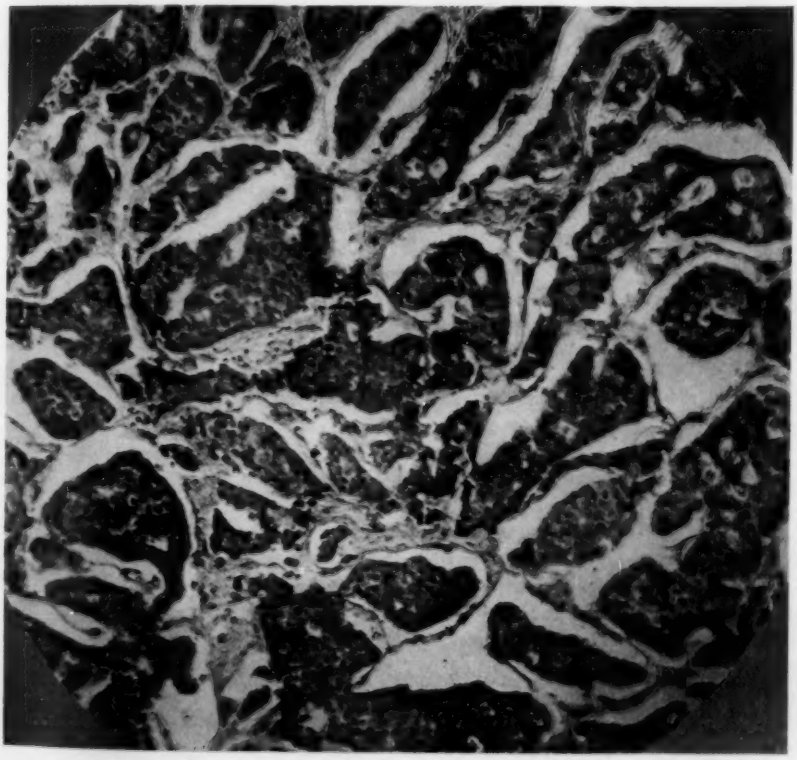

Fig. 2 (case 1).—Primary double cancer, showing the general architecture of the pancreatic tumor; × 300.

The cells were arranged either in small groups cut at different angles, forming tubules which resembled in size and arrangement the normal pancreatic acini, or in more diffuse masses. The latter were separated from one another by thin fibrous partitions approaching those seen normally between the pancreatic lobules. Mitotic figures were not uncommon. The stroma of the growth was similar to that of the normal pancreas.

At the edge of the tumor, there was a marked lymphocytic infiltration. In places, these formed regular follicles. The islands of Langerhans were hyperplastic. The ducts did not show changes of any kind. The metastases in the lungs and the liver closely resembled the pancreatic cancer.

It is judged that the tumor originated from the epithelial cells forming the acini.

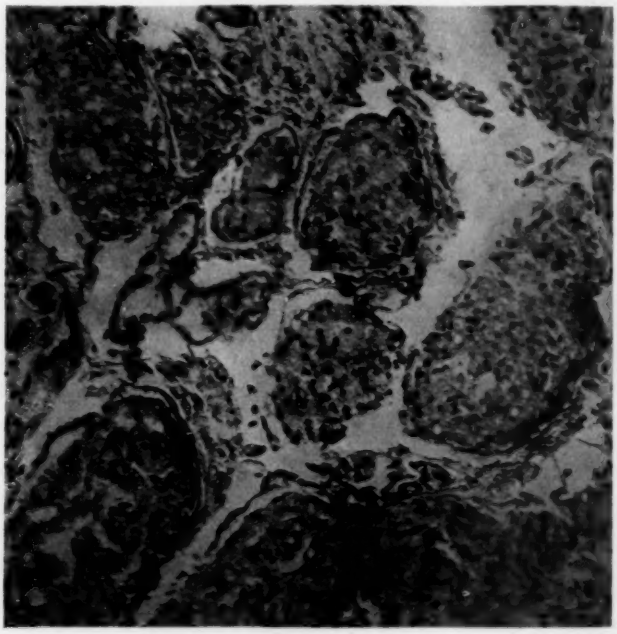

Fig. 3 (case 1).—Primary double cancer. Carcinoma of the prostate; × 80.

Prostate: The organ was somewhat larger and harder than that normally seen in persons of the patient's age. It was enclosed within its usual capsule, and its surface was regular and smooth. On cut surface, except for an apparent increase of the fibrous stroma, pathologic changes could not be seen with the naked eye.

The histologic examination showed a cancer in the early stages of its development (fig. 3). In the first place, only a few microscopic nodules characteristic of the epithelial malignant condition were found in the gland. Then, individual nodules showed pictures varying from a scant heaping up of the acinar epithelium with bare signs of a malignant disease to a complete obliteration of the glandular unit by malignant cells with or without rupture of the basal membrane. A few mitotic figures were seen. The fibrous stroma was largely increased. The acini not affected by malignant disease showed various degrees of irregular dilatation.

There were surprisingly few corpora amylacea. Lymphocytes infiltrated the organ throughout. Metastases could not be demonstrated in the tributary of far remote lymph nodes and other structures. The bones were not investigated.

The particular localization of the two cancers in the pancreas and in the prostate and their distinct histologic features show beyond any doubt that this case was one of primary double cancer. The prostatic cancer was of interest from two points of view. Microscopically, it illustrated a condition designated as "multicentric origin" of a cancer, that is, a cancer which starts in the same organ at different points at the same time. Thus it must be differentiated from "primary multiple cancer," the subject of the present communication.

Clinically, the case is of interest from the following standpoint: In cancer of the prostate, the gland is usually enlarged, irregular and hard as a stone; its surface may be elevated at different points by masses, which, when palpated individually, do not show the usual elasticity present in this organ. There is, however, another less common type of cancer of the prostate gland of which the case herein reported is an example. In this variety, the organ is only slightly enlarged, the enlargement being uniform without any irregularities. Even in the advanced stages of the disease, the gland is almost normal in size and in consistency, not causing symptoms referable to the urinary organs. Often the patient's complaints are compatible with a malignant disease present somewhere in the body, and the clinical attention is directed toward a metastasis which may occur early in this particular variety of cancer. At necropsy, such cancers are not infrequently missed, if the gland is not investigated with great care.

CASE 2.—*A widow, aged 51, with the complaints of pain in the perineum and uterine bleeding. Operation. Histologic disclosure of a primary double cancer; an epidermoid carcinoma of the cervix uteri and a colloid carcinoma of the anus.*

History.—The patient's past and family histories were unimportant. Nine years previously a fistula was opened near the anus and this had discharged a semipurulent material intermittently ever since. For a year and a half she had had steady aching pain in the rectum and perineum which had increased in severity. Five years previously, that is, two years after the menopause, she began to have a slight vaginal discharge and for this reason had a cervical dilatation and curettage at a hospital where she was told that malignant disease was not present. Since then, the discharge had persisted. Fifteen months previously, she had a definite uterine hemorrhage, a second one occurring five months previously. Since that time, she had had almost constant bleeding.

Examination showed her to be undernourished and ill. A small sinus was found opening just to the right of the anus. The margin of this was much indurated, irregular and hard and had a characteristic feeling of cancer. There was a hard mass palpable in the perineum and buttocks around the anus, about the size of an egg. On rectal examination, a hard tumor was felt involving the wall of the anal canal and partially obstructing it. Vaginal examination showed that this growth had involved the posterior vaginal wall.

Palpation of the cervix revealed a hard, irregular, cauliflower type of cancer. The growth did not extend to the vaginal vault, however, and the cervix was movable and was probably operable. Otherwise, the general physical examination was negative. A colostomy was performed; tissue was also removed from the cervix uteri for a histologic examination.

Microscopic Examination.—The tissue from the anus (fig. 4) was lined by squamous epithelium, which did not show any evidences of malignant disease. The tissue underneath the epithelium showed clumps of epithelial cells having a tendency to form alveoli. These were usually in close approximation to deeply staining mucoid material-colloid. Mitotic figures occurred frequently.

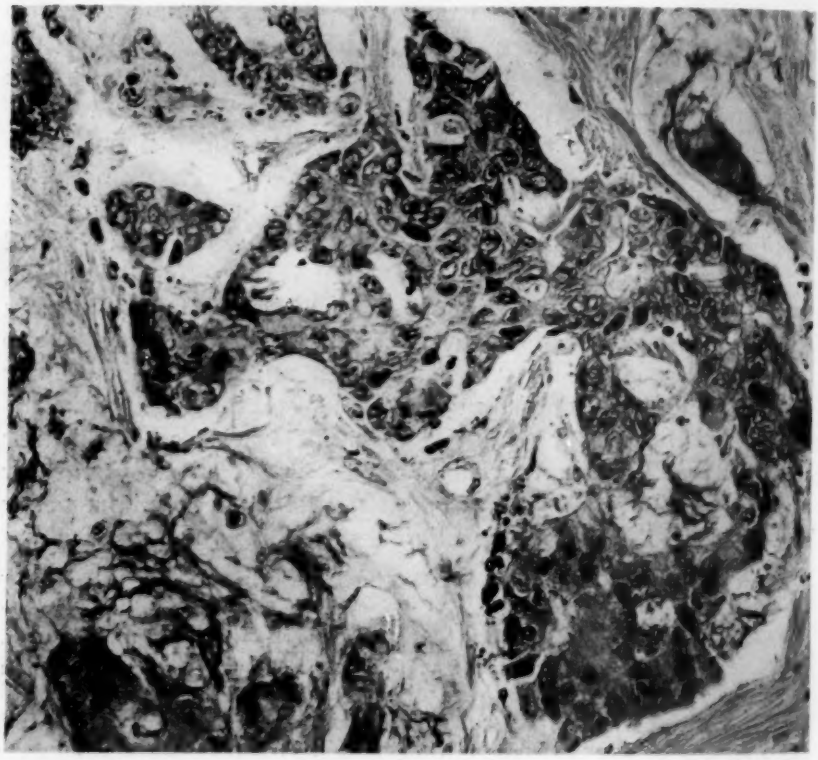

Fig. 4 (case 2).—Primary double cancer. Colloid carcinoma of the anus; × 300.

Tissue from the cervix uteri (fig. 5) showed a typical epidermoid carcinoma raising from the ulcerated squamous epithelium lining the cervical surface. Numerous cells were in mitoses.

The microscopic examination confirmed the clinical diagnosis of a primary double cancer. It was also apparent that the epidermoid cancer of the cervix uteri developed on top of a colloid adenocarcinoma of the anus which had existed for some time.

CASE 3.—A *single woman, aged 30, with the complaint of lumps in both breasts. Radical extirpation of both breasts. Histologic disclosure of a primary double cancer of both breasts.*

History.—The patient, a singer, whose past and family histories were unimportant, about three years previously noticed a small mass in her left breast which appeared soon after an injury to this organ. In two months the mass reached the size of a medium sized olive, but it almost disappeared under the influence of ten roentgen-ray treatments which she had received over a period of two years.

A year after the appearance of the first mentioned lump, she found another in the outer quadrant of the same breast. A surgeon examined her and found

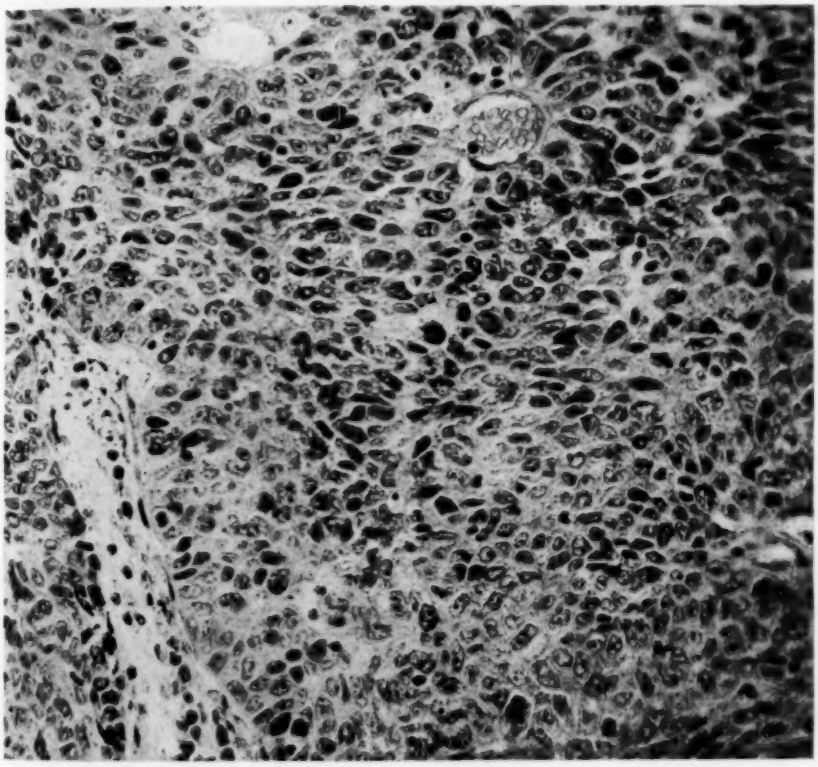

Fig. 5 (case 2).—Primary double cancer. Squamous epithelial cancer of the uterine cervix; × 300.

three small masses, two of which he removed. A report by a pathologist stated that the tissues did not show malignant disease. The healed wound of the removed tumor remained indurated and red, however. Eight months previously, she noticed the reappearance of a tumor in the original incision. Again she was examined by a surgeon who said that "it was turning into cancer". Shortly afterward, she found that glands had appeared in the left axilla. A week previously, she was referred to the hospital for an operation.

Examination of the left breast showed an ulcerated, hard mass at the site of two small incision scars in the outer and lower quadrants. It was obviously

a carcinoma. There were multiple large, firm, painless glands in the axilla and beneath the pectoral muscle. Not any glands were found above the clavicle. In the inner quadrant of the breast near the midline was an inconspicuous, indurated mass, which was adherent to the deep structures and over which the skin showed telangiectasis. This was the mass which received the massive roentgen-ray treatment.

In the right breast, just above the nipple, was a small, nodular, freely movable mass which was elevated, insensitive and hard. The skin was adherent to this mass. Two or three slightly enlarged, suspicious nodes could be felt at the right

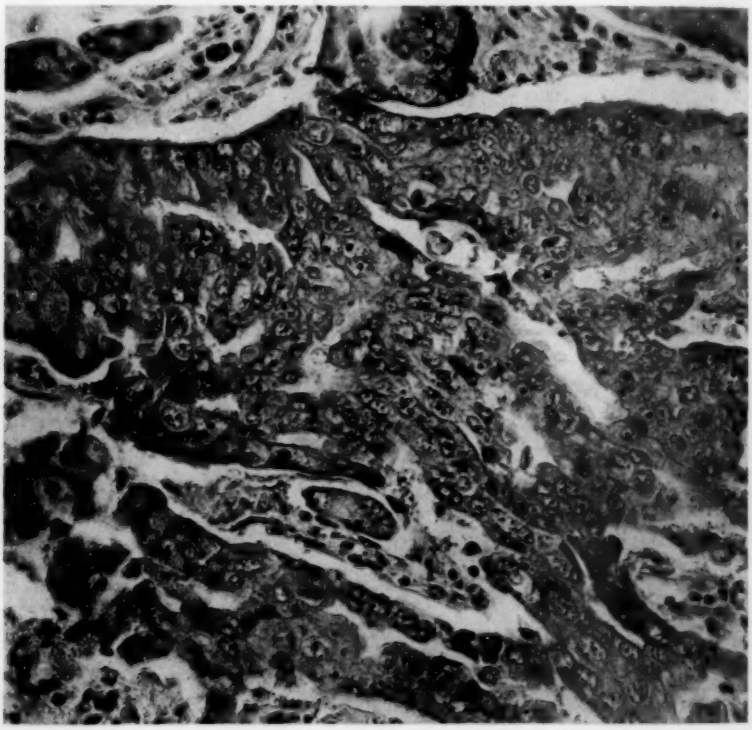

Fig. 6 (case 3).—Primary double cancer. Scirrhous cancer of the left breast; × 300.

pectoralis muscle but none higher up in the axilla. There was no retraction of the nipple of either breast.

Operation.—A usual radical operation was performed with the removal of both breasts. Grossly, enlarged nodes were not found in the left breast.

The patient made an uneventful recovery and was discharged twenty-one days after the operation.

Interval Course.—Two years after the removal of the breasts, the patient was "feeling very well and had gained 14 pounds (6.4 Kg.) in weight".

Microscopic Examination of the Removed Tumors.—Left Breast: The tumor (fig. 6) was made up of strands and diffuse agglomerations of large epithelial cells which occasionally formed tubular-like structures. This was embedded in a dense or edematous connective tissue stroma. Mitoses were seen here and there.

Right Breast: Here the tumor (fig. 7) was confined exclusively to the acini. In many areas the acini had still preserved their normal architecture, showing, however, a malignant transformation of their cells. In other places, the acini were replaced by diffuse cancerous nodules. There were few mitotic figures. A mucoid material, which was apparently colloid, could be seen here and there.

Accounts of the occurrence of double mammary cancers are found in treatises and in sporadic reports on diseases of the breast (Rodman,[6] Handley,[7] Davis [8] and Kilgore).[9] In the few cases, however, in which

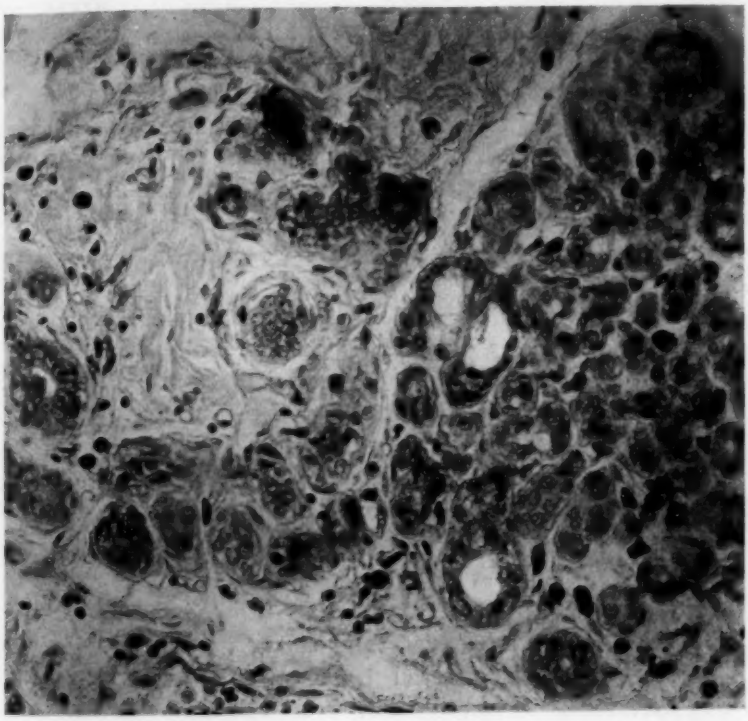

Fig. 7 (case 3).—Primary double cancer. Colloid adenocarcinoma of the right breast; × 300.

it is stated that the tumor started independently in each respective breast, the diagnosis is based on clinical data only. Kilgore,[9] for instance, in a series of 1,100 unselected mammary cancers, found 37, or 3.36 per cent, in which the malignant tumor was confined to both

6. Rodman, W. H.: Diseases of the Breast, Philadelphia, 1908.

7. Handley, W. S.: Cancer of the Breast, New York, Paul B. Hoeber, 1922.

8. Davis, Byron B.: Operative Results in Two Hundred Breast Tumors, Ann. Surg. **71**:270, 1920.

9. Kilgore, A. R.: The Incidence of Cancer of the Second Breast after Radical Removal of One Breast for Cancer, J. A. M. A. **77**:154 (Aug. 4) 1921.

breasts. Of these, he regarded 13 as probably primary double cancers. He based his opinion on the long interval between the occurrence of the two tumors, on the absence of recurrences of the first tumor, and also on the good results following the second operation. Those familiar with the ways in which mammary cancers sometimes metastasize will realize the fallacies of the clinical criteria taken alone.

The diagnosis of a primary double cancer of the breast in the present case was based on microscopic evidences. In the first place, the cancers varied in structure; that of the right breast was a scirrhous cancer, that of the left a colloid adenocarcinoma. In the second place, the tumors had apparently originated from different structures, the right cancer from the epithelium of the ducts, as most mammary cancers do, and the left from the acini. Figures 6 and 7 show clearly the striking histologic difference between the two tumors. Figure 7 illustrates an early proliferation of the acini with the transformation into a malignant condition. The nodule in this photomicrograph, moreover, displays all the characteristics of a primary and not a metastatic lesion.

Primary bilateral malignant disease may apparently occur in other paired or symmetrical organs, although only one case has been recorded in the literature. This was a case of a so-called "Schneeberger" cancer, that is, a primary bronchogenic cancer, a disease that occurs in a high percentage of workers in cobalt mines in the province of Saxony, Germany. In the left lung in this case, Beyreuther [10] found a columnar cell adenocarcinoma, in the right, a small squamous cell cancer. Neither of the tumors metastasized.

COMMENT

The idea of older pathologists, who attributed the occurrence of multiple cancers in one person to a cancerous "diathesis," is now abandoned. Today it is assumed that the underlying cause of double and single cancer is similar; and that the incidence of a multiple cancer in a person is merely a matter of "chance." The interest of this condition lies in its rarity as compared with the relative frequency of cancer in general.

There are two possible reasons for its rare occurrence.

The first plausible reason for the rarity of the primary multiple cancers may possibly be attributed to the state of immunity or resistance to cancer. Jensen [11] made it known that certain races of mice possess a natural immunity toward cancer. Following Jensen's observations,

10. Beyreuther, H.: Multiplicität von Carzinomen bei Einem Falle von sogenannten "Schneeberger" Lungenkrebs mit Tuberkulose, Virchows Arch. f. path. Anat. **250**:230, 1924.

11. Jensen, C. O.: Experimentelle Untersuchungen über Krebs bei Mausen, Centralbl. f. Bakteriol. O. I. **34**:28, 1903.

Ehrlich [12] produced evidences that a state of resistance to malignant tumors can be induced experimentally in rats and mice. Of particular interest are his so-called "cross experiments" (Zickzack Versuche), which are as follows: A cancer transplanted from a mouse to a rat continues to grow in the new host for about seven days, after which time it begins to regress until it finally heals. But the same tumor retransplanted in the early stages of its regression to a healthy mouse regains its former proliferative activity. Ehrlich noted that rats with healed mouse cancers resist a new "infection" with cancer. He finally demonstrated that mice with actively growing tumors are immune to secondary implants in most instances.

Although the intimate mechanism of natural or acquired resistance to cancer has not as yet been elucidated, the facts established by Ehrlich have been corroborated by numerous recent observers.[13] If one is then to suppose that man and animal display the same biologic peculiarities toward epithelial malignant disease, a person with an actively growing cancer ought to resist the development of a new one.

But it would be premature at present to attribute the rarity of primary double cancer in man to immunologic tendencies. In the first place, the immunity or resistance to cancer has been investigated in a few rodents only, and the results obtained are contradictory.[14] Moreover, the life cycle of these animals varies so much from that of man that analogies drawn between the two species would be misleading. Then again, the duration of the experimentally induced "immunity" is as yet a matter of controversy. Numerous observers, and more recently Gay,[15] working with the Flexner-Jobling rat tumor, found that rats bearing this growth could be readily reinoculated after the thirtieth day following their first inoculation. In still more recent studies, Sugiura and Benedict,[16] by repeating Ehrlich's experiments, also noted that in rats immunized against Flexner-Jobling carcinoma, the induced resistance steadily diminishes from approximately the seventh day after the inoculation; and that after the fourteenth day from the time of

12. Ehrlich, P.: Experimentelle Karzinomstudien an Mausen, Jena, 1906.

13. Murray, J. A.: Primary and Secondary Resistance to the Induction of Cancer, Eighth Scientific Report, The Imperial Cancer Research Fund, London, 1923.

14. Woglom, W. H.: The Study of Experimental Cancer, New York Columbia University Press, 1913; A Critique of Tumor Resistance, J. Cancer Research **7**:283, 1922. Wood, F. C.: Immunity in Cancer, Tr. Sect. Path. & Physiol., A. M. A., 1925, p. 122.

15. Gay, F. P.: A Transmissible Cancer of the Rat Considered from the Standpoint of Immunity, Fifth Report of the Cancer Commission of Harvard University, Boston, 1909.

16. Sugiura, R., and Benedict, S. R.: A Study of the Athreptic Theory of the Growth of Cancer, J. Cancer Research **10**:194, 1926.

the first inoculation with tumor these immune animals again become susceptible to reinoculation.

Whether a "cancerous allergy" exists in man and also whether a person affected with an actively growing tumor becomes "anergic" after a certain lapse of time, as does the experimental rodent, is entirely unknown. The relationship between the rarity of primary multiple cancer and resistance to cancer in man is therefore problematic.

The second possible cause for its rarity may possibly be due to the fact that a person with a cancer somewhere in the body succumbs to this disease before a second epithelial malignant tumor has had time to develop.

The majority of cases of multiple cancers found at necropsy occur in persons at or above the age of 70. Similar observations were noted in the animal kingdom, in which multiple tumors are much more frequent among the old.[17] This has been attributed to lack of resistance in those of advanced age as compared with younger persons who "fight" successfully against the development of a second epithelial malignant tumor (Siebke [2] and others). Such an explanation is, however, supported neither by experimental nor by clinical observations. In the laboratory, it has been noted that young animals are more suited for the development of an experimental cancer. In the clinic, it is an established observation that cancer is more rapidly fatal in younger persons that in those whose age is advanced. In the very old, the clinical course of a carcinoma is often a matter of years duration, due possibly to the low metabolic rate of the normal somatic as well as the malignant cells. In these persons, therefore, a second cancer may occasionally develop during the protracted course of the already existing epithelial malignant newgrowth.

SUMMARY

Three cases of primary double cancer are reported. According to statistics, this malignant condition occurs about once in 1,000 necrospies. It is assumed that the underlying cause of double and single cancer is similar. The interest of this malignant disease lies in its rarity as compared with the relative frequency of cancer in general. There are two plausible reasons for its rare occurrence: 1. A person with an actively growing cancer resists (immune ?) the implantation of a second cancer. 2. A person with a cancer somewhere in the body succumbs as a rule to this disease before a second malignant epithelial tumor has had time to develop.

The second possibility is apparently the dominating factor.

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17. Goodpasture, E. W., and Wislocki, G. W.: Old Age in Relation to Cell Overgrowth and Cancer, J. M. Research **28**:455, 1915-1916; Cohrs, P.: Ueber primäre Multiplizität von Geschwülsten bei Haustieren, Ztschr. f. Krebsforsch. **24**:156, 1927

EFFECT ON THE BLOOD PRESSURE OF THE RABBIT OF ARTERIOSCLEROSIS AND NEPHRITIS CAUSED BY URANIUM

INFLUENCE OF OTHER HEAVY METALS *

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In a preliminary publication,[1] it was stated that a severe arteriosclerosis is produced in the rabbit by certain samples of uranium nitrate. The suggestion was made that an impurity might be present in some samples which might in some way be responsible for those observations. Before the experiments were completed, careful consideration was given to all the possible impurities of commercial uranium preparations, and in order to save time it was decided to try, by direct experiment, the influence of two of them: radium and vanadium—the first, because it is the most obvious impurity of uranium, particularly in old preparations;[2] the second, because the literature on vanadium poisoning is meager.[3]

The idea of an impurity, however, soon became untenable on account of subsequent results with uranium alone, as all four samples used were found to produce severe arteriosclerosis occasionally. The experiments with uranium mixtures were, nevertheless, carried further and are now reported together, since they are not without interest; besides, they constitute a good control of the main part of the investigation. One of the rabbits which developed uranium arteriosclerosis had received lead carbonate by mouth some time before, and although lead had not been administered in the other positive cases, there were some differences (to be emphasized later) which required reexamination of the effect of a previous treatment with lead on uranium intoxication. The blood pressure of half of the animals was measured almost daily, before the intoxication and during the whole length of the experiment.

This, then, is a report of the observations on the pathologic processes and the blood pressure in rabbits subjected to intoxication caused by uranium alone and in association with lead, radium and vanadium.

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* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. Dominguez, R.: Science **64**:407, 1926.
2. Boltwood, B. B.: Am. J. Sc. **20**:239, 1905.
3. Hamilton, A.: Industrial Poisons in the United States, New York, The Macmillan Company, 1925.

MATERIAL

Sixty-six rabbits were used in these experiments. Carotid loops for the purpose of measuring the blood pressure (Van Leersum) were made in forty-eight (*D*, second column, table 1). Good loops were obtained in thirty-two, and the blood pressure was measured almost daily in all these. Details concerning this method of taking the blood pressure and the results arrived at in the normal rabbit are to be found elsewhere.[4]

Four samples of uranium nitrate were used. These samples were obtained from Eimer and Amend, New York; Merck and Co., Germany; Mallinckrodt Chemical Works, St. Louis, and J. T. Baker Chemical Company, Phillipsburg, N. J., and are referred to in the following as *Ur* 1, *Ur* 2, *Ur* 3 and *Ur* 4, respectively. The surface activity of these samples, tested in an α-ray electroscope, gave ambiguous results, but this method was not considered sufficiently accurate for the purpose.

Radium was purchased from the Radium Chemical Company, Pittsburgh, 1 mg. of radium bromide in 10 cc. of distilled water, and vanadium chloride from Merck and Co., New York.

The uranium nitrate was injected under the skin on the back of the rabbit in concentrations of 1:5,000, 2:1,000 and 5:1,000 in distilled water, once or twice a week. Some animals developed calcified nodules at the site of the injections. Radium was injected subcutaneously in convenient dilutions prepared from the original 10 cc. by means of a pipet calibrated to the hundredth of 1 cc., the amount of radium bromide contained per cc. being calculated as of the order of 1×10^{-5}, 2×10^{-5}, 4×10^{-5} and 1×10^{-4} mg. in the different solutions used. These radium solutions were not all made at once, but were prepared in 50 cc. volumes at a time. In some of these radium solutions, uranium nitrate was dissolved in 2:1,000 concentration. From time to time, 0.5 cc. was taken from the bottles (a different pipet being used every time) and allowed to dry on a flat dish or a piece of window glass. The activity of these plates was then tested in an ordinary gold-leaf electroscope, the rate of fall being measured with a stopwatch. The result of one measurement is shown. The solutions were supposed to contain 2 mg. of uranium and 1×10^{-4} mg. of radium per cubic centimeter, and the drying surface, a circle marked out with a wax pencil, was 3.8 cm. in diameter.

Ra (residue of 0.5 cc.) 36.1 divisions per minute
Ur 1 + Ra (residue of 0.5 cc.) 36.4 divisions per minute
Ur 4 + Ra (residue of 0.5 cc.) 45.1 divisions per minute
Ur 1 (residue of 0.5 cc.) 0.67 divisions per minute
Ra standard (1.1×10^{-3} mg. Ra in sealed glass tube 1 mm. thick) 10.5 divisions per minute
Natural leak, 0.25 divisions per minute

Taking into account the natural leak, one sees that the activity of the uranium-radium solution was from eighty to 100 times that of uranium alone. If the plate containing the radium residue was covered with a sheet of writing paper, its activity was reduced to 0.7 divisions per minute. The precise amount of radium in solution was not of interest here. All that was required was to increase the radioactivity of the uranium sample injected and observe the direction of the injurious effect produced by it. A local effect was not observed in the animals which received only radium solutions or radium solutions to which uranium had been added.

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4. Dominguez, R.: J. Metab. Research. **6**:123, 1924; J. Exper. Med. **46**:443 1927.

Vanadium chloride solution, on the other hand, was irritating to the skin in concentrations greater than 1:1,000. The fresh solution was blue, but it changed to green in a few minutes. In a few days the vanadium precipitated, so that the solution had to be made fresh immediately before use. The local reaction was the same, whether the blue or the green solution was injected. In the few animals which received uranium and vanadium, each substance was injected separately in a different side.

Lead was given in two forms: lead carbonate smeared on carrots, by mouth, daily, and lead acetate in watery solution (from 1 to 4 per hundred cubic centimeters), by stomach tube, once or twice weekly.

The animals were kept in separate cages, and were fed their usual diet of oats, hay and greens. The body weight was taken every time the injections were made, that is, once or twice every week. After death, the autopsy was carefully performed, special attention being given to the circulatory system and the kidneys. The aorta and pulmonary and main branches were opened and the latter followed as far as possible. A few of the aortas and many of the kidneys were sectioned (frozen section and paraffin embedding) and examined microscopically. In one case (rabbit 17) the brain, heart, thyroid, spleen, liver and kidney were sectioned and examined.

GENERAL RESULTS

The main data of the experiments have been arranged in table 1. The animals of each group have been placed in the order of increasing duration of the experiment, the duration being estimated from the day of the first dose of the toxic material administered to the animal until death. The animals will be referred to by the numbers of the first column.

A few details concerning the way some of the mixed intoxications were conducted will be given next.

Rabbit 17 received lead carbonate by mouth (daily dose gradually increased from 14 to 300 mg.) during the first 180 days. The lead experiment was discontinued because four animals (rabbits 60, 61, 62 and 63) had already come to autopsy and were found to be free from obvious lesions. After ninety-five days, the injections of uranium were started.

Rabbit 18 received 2.40 Gm. of lead acetate in twenty-five days. Four days after the last dose, the injections of uranium were started.

Rabbits 19, 20, 21 and 22 received lead acetate by stomach tube and radium by injection in the first 213, 216, 219 and 216 days, respectively; uranium in the last 96, 120, 120 and 120 days, respectively.

Rabbit 36 received four injections of vanadium in the last thirty days of the experiment.

Rabbit 37 received injections of vanadium during the first 126 days; from then on both vanadium and uranium were administered.

Rabbits 16 and 33 were given uranium alone during the first 235 days of the experiment; uranium and radium were given in the remaining days. The other experiments do not require explanation.

Three rabbits died after one or two injections of uranium (rabbits 2, 38 and 39), and their death was unexplained. Two were given a large initial dose to determine the effect of acute uranium intoxication on the

TABLE 1.—*Summary of Experiments*

Experiment	No.	Sex	Duration of Experiment, Days	No. of Injections of Uranium	Total Amount Administered: Uranium, Mg.	Lead, Gm.	Radium 10^{-4} Mg.	Vanadium, Mg.	Interval Between Last Dose and Death, Days	Weight (Kg.): Initial	Final	Aorta	Pulmonary	Aortic Branches	Kidneys	Blood Pressure Taken	Remarks
Ur 1	1*	M	7	2	10.0	....	....	....	3	3.060	2.800	0	0	0	Swollen	Yes	Acute intoxication
	2*	F	12	2	0.4	....	....	....	4	3.320	.....	0	0	0	.....	Yes	
	3	F	76	9	2.14	....	....	....	6	3.460	3.115	++	+	+	.....	Yes	
	4	F	88	10	2.32	....	....	....	18	3.355	2.340	++	+	+	Calcified	Yes	
	5	M	133	21	74.0	....	....	....	17	2.680	2.020	++	+	+	Calcified	Yes	Double suprarenalectomized
	6	M	147	13	2.57	....	....	....	4	3.350	2.670	0	0	0	.....	Yes	Killed
	7	M	355	40	151.0	....	....	....	47	2.160	1.350	+	0	0	.....	Yes	
	8	F	365	48	151.5	....	....	....	10	2.670	1.715	0	0	0	Small	Yes	
	9	F	535	76	196.1	....	....	....	2	2.460	1.745	0	0	0	Small	Yes	
	10	M	572	88	452.5	....	....	....	2	2.340	2.400	0	0	0	.....	No	Killed
Ur 1 and Pb acetate	11*	M	57	2	0.4	2.18	....	....	5	2.880	1.975	0	0	0	.....	Yes	
Ur 1 and Ra	12*	F	62	5	6.5	....	0.5	....	6	2.315	2.125	+	0	0	Pitted	No	
	13	F	175	19	59.0	....	3.1	....	1	2.265	2.275	+	0	0	.....	No	
	14	F	307	33	113.0	....	14.2	....	6	3.705	3.140	0	0	0	.....	No	
	15	F	339	42	166.0	....	19.3	....	4	2.185	2.750	0	0	0	.....	No	Killed
Ur 1, then Ur 1 and Ra	16	M	428	58	168.0	....	3.9	....	5	2.320	1.665	+	0	+	.....	Yes	
Pb carbonate, then Ur 1	17	M	431	9	6.75	11.55	....	....	52	2.225	.....	++	+	+	Calcified	Yes	
Pb acetate, then Ur 1	18	F	84	8	5.0	2.40	....	....	5	3.275	2.885	0	0	+	.....	Yes	Killed
Pb acetate and Ra, then Ur 1	19	M	339	16	63.0	4.77	12.7	....	4	2.455	2.500	0	0	0	Pitted	No	Killed
	20	M	343	15	53.8	4.49	13.5	....	8	2.985	2.900	0	0	0	.....	Yes	Killed
	21	M	343	22	81.8	5.96	13.5	....	8	3.425	2.840	0	0	0	.....	Yes	Killed
	22	F	343	22	81.8	4.68	14.3	....	8	3.470	3.115	+	0	0	.....	Yes	Killed
Ur 2	23*	F	6	2	10.0	....	....	....	2	2.650	.....	0	0	0	Swollen	Yes	Acute intoxication
	24	,,	53	8	1.8	....	....	....	5	2.215	1.800	+	0	+	Pitted	No	Killed
	25	F	79	14	45.0	....	....	....	3	3.010	2.870	+	0	+	.....	Yes	
	26	M	113	20	72.0	....	....	....	4	2.180	2.080	0	0	0	.....	No	
	27	F	153	22	7.6	....	....	....	5	2.370	1.890	+	0	+	Granular	No	Meningitis
	28	M	200	26	73.0	....	....	....	15	2.080	1.125	0	0	0	Granular	Yes	
	29	M	344	40	63.8	....	....	....	3	1.950	1.265	+	0	+	Granular	No	
	30	M	355	48	220.0	....	....	....	17	3.280	2.145	0	0	0	.....	No	
	31	F	396	63	156.8	....	....	....	2	2.475	1.615	0	0	+	Granular	No	
	32	F	533	76	238.8	....	....	....	12	2.525	1.585	++	0	+	.....	No	

Ur 2, then Ur 2 and Ra.....	33	F	579	84	327.0	....	30.9	....	9	2.500	1.985	0	0	0	Small	Yes	Killed
Ur 2 and Ra.....	34	M	339	42	131.2	....	27.3	....	4	2.405	2.660	0	0	0	.....	No	Killed
	35	M	343	42	170.0	....	27.7	....	8	2.430	2.560	0	0	0	.....	No	Killed
Ur 2, then Ur 2 and Va.....	36	M	495	66	269.0	....	....	20.0	2	2.510	1.780	+	+	0	.....	Yes	
Va, then Va and Ur 2.....	37	F	233	8	12.0	....	....	74.0	2	2.835	1.740	+	0	0	Granular	Yes	
Ur 3.....	38*	M	5	1	0.5	....	....	....	5	2.025	.....	0	0	0	.....	No	
	39*	F	6	1	0.2	....	....	....	6	1.785	.....	+	0	0	Pitted	No	
	40*	M	6	1	0.5	....	....	....	6	2.340	.....	0	0	0	.....	No	Killed
	41	..	85	13	3.9	....	....	....	1	2.760	1.850	++	+	+	.....	No	
	42	F	307	47	88.3	....	....	....	9	2.320	1.755	++	0	+	Calcified	No	
	43	F	535	73	223.2	....	....	....	10	2.105	1.420	0	0	0	.....	No	
	44	F	535	76	253.8	....	....	....	10	2.240	1.785	+	+	0	Calcified	No	
Ur 4.....	45	M	190	33	132.5	....	....	....	5	2.485	2.750	0	0	0	Swollen	No	
	46	F	353	50	206.0	....	....	....	5	2.330	1.860	++	+	+	Calcified	Yes	
	47	F	572	88	451.5	....	....	....	2	2.325	2.575	+	0	0	.....	No	Killed
Ur 4 and Ra.....	48	F	188	18	57.5	....	4.6	....	8	3.575	3.045	0	0	0	.....	No	Killed
	49	M	315	31	97.0	....	11.7	....	21	2.575	1.230	++	0	0	.....	No	
	50	F	337	47	190.0	....	51.4	....	2	2.920	2.030	0	0	0	.....	Yes	Killed
	51	F	338	42	156.0	....	33.9	....	3	2.175	2.035	0	0	0	Granular	No	Killed
	52	F	338	42	167.0	....	38.95	....	3	2.435	3.050	0	0	0	.....	No	Killed
Ra.....	53	F	155	..	.....	....	3.5	....	2	1.775	2.445	+	0	0	.....	No	
	54	F	264	..	.....	....	13.7	....	5	3.255	3.490	0	0	0	.....	No	
	55	M	341	..	.....	....	30.4	....	6	2.945	3.050	0	0	0	Pitted	No	Killed
	56	F	341	..	.....	....	33.4	....	6	3.110	3.700	0	0	0	.....	Yes	Killed
	57	M	344	..	.....	....	35.3	....	9	2.225	2.950	0	0	0	Pitted	Yes	Killed
Ra and lead acetate.....	58	F	188	..	.....	2.53	8.7	....	4	2.255	2.600	+	0	0	.....	No	Pneumonia
Lead acetate.....	59	F	19	..	.....	1.70	....	....	2	2.550	2.430	+	0	..	.....	Yes	
Lead carbonate.....	60	M	56	..	.....	1.45	....	....	2	1.680	1.735	0	0	..	Pitted	Yes	Pneumonia
	61	M	179	..	.....	1.34	....	....	137	2.140	2.555	0	0	..	.....	Yes	Killed
	62	M	183	..	.....	11.92	....	....	4	2.550	2.270	0	0	..	Pitted	Yes	Mediastinal abscess
	63	M	202	..	.....	8.30	....	....	22	1.990	1.695	0	0	..	.....	Yes	Pneumonia
Va.....	64	F	235	..	.....	....	....	149.5	4	2.840	3.230	0	0	0	.....	No	Killed
	65	F	237	..	.....	....	....	157.0	6	2.565	2.575	0	0	0	.....	Yes	Killed
	66	M	237	..	.....	....	....	161.7	6	2.720	2.430	0	0	0	.....	No	Killed

* Received less than eight injections of uranium.

blood pressure (rabbits 1 and 23). Two died of an intercurrent pneumonia (rabbits 11 and 12) early in the experiment. Another became paralyzed and was killed (rabbit 40). Although these eight animals do not properly belong in a study of chronic intoxication, they have been retained because they afford a natural control to the lesions found in the other animals. When these eight animals are excluded (number marked with an asterisk in table 1), forty-four remain which were subjected to uranium intoxication, of which twenty-seven died naturally (whether as a result of the intoxication or of an intercurrent disease) and seventeen were killed. The duration of the first twenty-seven experiments varied from 76 (rabbit 3) to 535 days (rabbits 9, 43 and 44), the total amount of uranium given varying from 2.14 (rabbit 3) to 269 mg. (rabbit 36). The duration of the remaining seventeen varied from 54 (rabbit 18) to 579 days (rabbit 33), the amount of uranium varying from 1.8 (rabbit 24) to 452.5 mg. (rabbit 10).

That the animals developed an increased resistance to uranium as the intoxication proceeded, I take as established. For instance, in the last twenty-three days of the experiment, rabbit 10 received 50 mg. of uranium nitrate in seven injections. The only effect noted was a drop in weight from 2.68 to 2.40 Kg. In the last twenty-nine days, rabbit 22 received 44 mg. in seven injections; the weight dropped from 3.26 to 3.11 Kg.

Of the twenty-seven animals that died as a result of the intoxication, eighteen lost more than 500 Gm. (67 per cent); six lost less than 500 Gm.; two gained; in one (the first animal of the series, rabbit 17), the record is incomplete. The greatest loss in weight was exhibited by rabbit 49, 1.345 Kg. Its best weight was the initial weight, 2,575 Kg. Of the seventeen animals killed in the course of the experiment, five lost more than 500 Gm. (29 per cent), the greatest loss in weight being 890 Gm. (rabbit 50); five lost less than 500 Gm., and seven gained. It is impossible to give more details on this question, because the age of the animals was unknown and the experiments have been heterogeneous in character, duration and amount of uranium. But a certain relation has been found between the loss in weight and the presence of other lesions in the body, to which attention will be called later. The loss in weight was of two general types: either the weight began to fall soon after the first injection and continued to fall progressively until death, or the weight oscillated about a certain level for a considerable time and then fell, more or less rapidly, before death. The former type is considered here as having significance. In some instances the animals easily recovered from a fall in weight if the injections were interrupted or the dose of uranium was diminished; in others, however, the weight continued to fall in spite of these measures, and the animals reached a state of profound emaciation (rabbits 7 and 49).

Three animals died under acute respiratory distress, undoubtedly owing to a terminal renal acidosis (rabbits 3, 4 and 5).

Rabbit 37, referred to previously, showed, a few days after the third injection of uranium and vanadium, a spasticity of the hind legs; rather quick recovery followed. The weight dropped from 2.88 to 2.14 Kg. in seven days. After the fourth injection of uranium and vanadium, the right hind leg became paralyzed, but recovered. Although the injections were given at long intervals and in small amounts, the animal lost 1.06 Kg. in eighty-seven days, after six doses of uranium and vanadium. The paralysis reappeared after the seventh injection, and the animal died two days after the eighth injection. There was not any disturbance of the sphincters, and the cord was normal grossly. This is the only observation of its kind I have recorded.

TABLE 2.—*Frequency of Spontaneous Arteriosclerosis in the Rabbit*

Author	No. Rabbits Examined	Positive Cases	Percentage
Hedinger and Loeb: Arch. f. exper. path. u. Pharmakol. **56**: 314, 1907	About 100	0	0
Miles: J. A. M. A. **49**: 1173, 1907	49	17	34.7
Lucien and Parisot: Compt. rend. Soc. de biol. **64**: 917, 1908	200	10	5
Benecke: Virchows Arch. f. path. Anat. **191**: 208, 1908	400	12	3
Pearce: J. A. M. A. **51**: 1056, 1908	51	3	6
Weinberg: Compt. rend. Soc. de biol. **65**: 561, 1908	562	37	6.6
Hill: Arch. Int. Med. **5**: 22, 1910	210	31	14.8
Levin and Larkin: Proc. Soc. Exper. Biol. and Med. **7**: 109, 1910	240	31	12.9
Ophüls: Proc. Soc. Exper. Biol. and Med. **8**: 75, 1911	50	0	0
Loeb: Arch. f. exper. Path. u. Pharmakol. **69**: 114, 1912-1913	429	0	0
Van Leersum: Virchows Arch. f. path. Anat. **217**: 452, 1914	132	4	3
Saphir: Am. J. Path. **1**: 403, 1925	50	3	6
Goldblatt: Unpublished data	201	31	15.4

Results of the autopsy of the animals which received radium, vanadium or lead, in the doses used, were essentially negative.

The lesions found at autopsy on animals which received uranium alone or combined with other metals will be considered separately later. They involve the aorta, pulmonary artery, aortic branches, kidney, stomach wall and general musculature of the body. But before presenting these observations I shall review the question of spontaneous arteriosclerosis in the rabbit, and at the same time consider the sclerosis produced by intravenous injections of epinephrine hydrochloride.

SPONTANEOUS ARTERIOSCLEROSIS IN RABBITS

The data which I have been able to analyze myself on spontaneous arteriosclerosis in rabbits are presented in table 2.

Other data to which I have not had access are as follows: cases mentioned in Lucien and Parisot's table,[5] without reference to the original; report of experiments on eighteen rabbits by Thévenot

5. Lucien, M., and Parisot, J.: Compt. rend. Soc. de biol. **64**:917, 1908.

(5.5 per cent positive); report of experiments on twenty-five rabbits by Giovanni-Quadri (8 per cent positive); report of experiments on thirty rabbits by Kalamkarov (10 per cent positive), and the report by J. L. Miller [6] of Mironescu's experiments on 300 normal rabbits without evidences of changes. Other data not suited for the table are those of Steinbiss [7] who says, "Ich habe seit dem Begin meiner Versuche 1908 jede Gelegenheit wahrgenommen, nach Spontansklerose beim Kaninchen zu suchen, habe mir ausser den mir bei meinen Material vorkommenden Todesfällen und Tötungen aus andern als dem mit meinen experimenten zusammenhängenden Gründen vielfach Herz und Aorta von Schlachttieren verschafft, so das ich über 500 Beobachtungen an über 3 Monate alten Tieren verfüge." (Since beginning my experiments in 1908, I have taken advantage of every opportunity to look for spontaneous sclerosis in the rabbit, and, in addition to my own animals that have died or have been killed, I have, in a number of instances and for reasons other than those connected with my experiments, procured the heart and aorta of slaughtered animals, so that I now possess 500 observations on animals more than three months old.) It is probable that by "slaughtered animals" Steinbiss means rabbits. Van Leersum [8] and Shapiro [9] interpret it thus. In any case, he finds only two doubtful cases of spontaneous lesions. Brown, Pearce and Van Allen,[10] who found sixteen lesions of the aorta in 350 male rabbits, add in a footnote: "The majority of the lesions of the aorta occurred in the first 100 rabbits and most of them were comparatively slight degenerations. Subsequently only marked lesions were recorded." Their 4.6 per cent does not represent the totality of the gross lesions observed, and the authors do not explain what is meant by "marked lesions."

Clarkson and Newburgh [11] state, after examination of the aortas of 100 rabbits from laboratory stock, that "a certain type of abnormality was not infrequent. This lesion always occurred in the region of the arch. It was uniformly small, being about 1.5 mm. in diameter. It was a very white, slightly raised process with a depression in its center." Finally, there are abundant reports of attempts to produce lesions with a variety of means, in which no lesions were obtained. This material will not be considered here, but if the naturally occurring arterial lesions in

6. Miller, J. L.: Spontaneous Arterial Degeneration in Rabbits, J. A. M. A. **49**:1789 (Nov. 28) 1907.

7. Steinbiss, W.: Virchows Arch. f. path. Anat. **212**:152, 1912.

8. Van Leersum, E. C.: Virchows Arch. f. path. Anat. **217**:452, 1914.

9. Shapiro, S.: J. Exper. Med. **45**:595, 1927.

10. Brown, W. H.; Pearce, L., and Van Allen, C. M.: J. Exper. Med. **42**:163, 1925.

11. Clarkson, S., and Newburgh, L. H.: J. Exper. Med. **43**:595, 1926.

the rabbit were as common as some authors believe, negative experiments would be less frequent than they actually are.

Table 2, as it stands, represents an important amount of data from different countries, extending over twenty years. The best compilation, in my opinion, is Weinberg's, not only on account of the number, but because his 562 rabbits were "destinés à l'alimentation," and, therefore, not subjected to any experimental procedure. His animals were in three lots, 516, 21 and 25, and the percentage of arteriosclerosis was 6, 19 and 4, respectively. In 130 more rabbits, which had been used for different experiments, he found 9 cases of aortic lesions (6.9 per cent). The total would give 692 rabbits, 46 with arteriosclerosis (6.6 per cent). The most important statistics, from my immediate point of view, are Dr. Goldblatt's, since he has worked in the same building with me (department of pathology), and his rabbits came from the immediate vicinity of Cleveland, like mine, although from different dealers. Besides the aorta, he has examined systematically the pulmonary artery and the main aortic branches, obtaining negative results. His search has been invaluable to me. My own cases were in forty-eight rabbits, of which only a few were not experimented on. The others were subjected to double suprarenalectomy or guanidine intoxication, or they died during the preparation of the carotid loop or as the result of an intercurrent disease. Among these forty-eight rabbits, I found seven with arteriosclerosis of the common type (14 per cent), namely, discrete patches in the ascending arch. In one a few patches were also present in the transverse portion of the arch and in the abdominal aorta. Lesions were not found in the pulmonary or aortic branches in any of the animals.

The statistics of Miles stand out on account of the exceptional frequency of the spontaneous lesions. Her work was published at the peak of the enthusiasm created by Josué's discovery,[12] and many thought that it appeared to disprove the reality of arteriosclerosis caused by epinephrine hydrochloride. As time passes, however, and more normal rabbits are examined, her results appear to have been local, which demands explanation as well as confirmation. Now and then, a suggestion is offered. Thus, for instance, à propos of Crawford's work [13] on "loco-weed disease," an editorial in the *Journal* of the American Medical Association [14] reads, "May not the greater frequency of this 'spontaneous' degeneration in Colorado be due to the forage plants of the region containing minute amounts of some mineral poisons (possibly

12. Josué, O.: Compt. rend. Soc. de biol. **55**:1374, 1903.

13. Crawford, A. C.: United States Department of Agriculture, Bureau of Plant Industry, 1908, Bull. 129.

14. Radium a Cause of Loco-Weed Disease, editorial, J. A. M. A. **51**:1338 (Oct. 17) 1908.

barium among them) taken up from the soil?" But the work of Marsh, Alsberg and Black [15] does not support Crawford's idea, and the suggestion in the editorial just quoted proved negative in the hands of Hill,[16] as far as an injurious effect of barium chloride on the aorta is concerned. Uranium could logically be suggested now, but if I were to suggest anything, it would be to repeat Miles' work and see if the next 49, or better 100, rabbits in Colorado show again a high percentage of arterial lesions.

The nature of the lesions is not as discordant as their frequency. The large majority consists in a few small discrete patches situated in the thoracic aorta, in the arch especially. In a few cases the lesions involved the whole length of the aorta: two in Miles' collection and three in Lucien and Parisot's. One of Weinberg's rabbits had many small calcareous plaques in the thoracic and first portion of the abdominal aorta, accompanied by dilatation of the vessel; and one of Hill's, a young rabbit weighing 940 Gm., had a lesion appearing "as a diffuse roughening of the thoracic and upper abdominal aorta." Pearce [17] has presented, besides the fifty-one rabbits of the table, eleven more which received substances of one kind or another (dog's serum, nephrotoxic serum, human blood, typhoid bacillus, chrome salts), and four of them showed lesions. In two of these rabbits "the lesions were diffuse involving irregularly the entire aorta and comparable to those produced by adrenalin." If I put Pearce's additional 11 rabbits in the table, I obtain out of 183 positive cases 9 in which the lesion was extensive or severe.

The lesion that is found spontaneously and that which is produced by intravenous injection of epinephrine hydrochloride consist essentially in a calcification of the aortic media, like the lesions here reported. It will be of some use then, to summarize briefly the observations in sclerosis from epinephrine hydrochloride. Saltykow's [18] exhaustive review has been of considerable assistance to me, but I have consulted the original whenever the lesion seems to be at all extensive. Cases in which the totality of the aorta was involved are few: one each reported by Pic and Bonnamour,[19] Külbs,[20] Lortat-Jacob and

15. Marsh, D. C.; Alsberg, C. L., and Black, O. F.: United States Department of Agriculture, Bureau of Plant Industry, 1912, Bull. 246.

16. Hill, M. C.: Various Forms of Experimental Arterial Disease in the Rabbit, Arch. Int. Med. **5**:22 (Jan.) 1910.

17. Pearce, R. M.: Occurrence of Spontaneous Arterial Degeneration in the Rabbit, J. A. M. A. **51**:1056 (Sept. 26) 1908.

18. Saltykow, S.: Centralbl. f. allg. Pathol. u. path. Anat. **19**:321 and 369, 1908.

19. Pic. A., and Bonnamour, S.: Compt. rend. Soc. de biol. **57**:219, 1905.

20. Külbs: Arch. f. exper. Path. u. Pharmakol. **53**:140, 1905.

Sabaréanu,[21] Scheidemandel,[22] Loeb and Githens,[23] Bonnamour and Thévenot,[24] except Lortat-Jacob and Sabaréanu [21] who had three or four cases (description incomplete, no illustrations), involving a total of about nine rabbits. The most intense of these cases seems to be the one reported by Scheidemandel, according to whose description the aorta was transformed into a rigid, beaded tube, "welches sich am besten mit den bekannten Bildern einer stark verkalkten, gänsetracheen-artigen Femoralarterie des Menschen vergleichen lässt" (which may be best compared with the well known pictures of a markedly calcified femoral artery in man, resembling the trachea of a goose). In this same animal Scheidemandel saw a calcification in rings (ringförmige Mediaverkalkung) in the branches of the pulmonary arteries, but no calcification of the aortic branches, although he describes a thickening of their walls. Lesions in the peripheral arteries are infrequent in sclerosis caused by epinephrine hydrochloride.[18] Of the innumerable experiments reported on arteriosclerosis induced by other means, I shall mention only two. One was reported by Israel [25] (extirpation of one kidney and repeated injections of alcohol in the remaining one), whose description is as follows: "Die Kalkplatten finden sich überwiegend an der vorderer Hälfte im aufsteigenden und unteren Brusttheil der Aorta, an der Hinteren im oberen Brusttheil, während Bogen und Bauchtheil relativ frei sind." (The calcified plaques are found chiefly in the anterior portion of the ascending aorta and the lower thoracic aorta, and in the posterior portion of the upper thoracic aorta, whereas the arch and the abdominal aorta are relatively free.) The description is accompanied by a good illustration. The other case was reported by Hedinger and Loeb;[26] besides the calcified plaques of one of their rabbits (subcutaneous injections of potassium iodide) transverse striations were found in the aorta.

Summary.—Spontaneous arteriosclerosis in the rabbit varies from place to place, being in some localities rare or absent, in others, Colorado in particular, frequent. The mean of more than 3,500 rabbits examined during the last twenty years in this country and in Europe is less than 6 per cent. The proportion of severe cases among normal rabbits is rare (about 4 per cent of the positive cases, less than 0.3 per cent of the total). The pulmonary and peripheral arteries, with the exception of

21. Lortat-Jacob, L., and Sabaréanu, G.: Compt. rend. Soc. de biol. **58**:583, 1905.

22. Scheidemandel, E.: Virchows Arch. f. path. Anat. **181**:363, 1905.

23. Loeb, L., and Githens, T. S.: Am. J. M. Sc. **130**:658, 1905.

24. Bonnamour, S., and Thévenot, L.: Compt. rend. Soc. de biol. **66**:387, 1909.

25. Israel, O.: Virchows Arch. f. path. Anat. **86**:299, 1881.

26. Hedinger, E., and Loeb, O.: Arch. f. exper. Path. u. Pharmakol. **56**:314, 1907.

the iliacs, are not affected. In the vicinity of Cleveland, the frequency of the lesions during the past three years has been about 15 per cent, all having been minimal or slight (single or conglomerate patches, with and without calcification, at the arch of the aorta).

In regard to sclerosis caused by epinephrine hydrochloride, I shall stress the following points: the cases in which the totality of the aorta is involved have been rare (less than 3 per cent in about 400 reported experiments, approximate figures); the pulmonary and peripheral arteries are rarely affected; aneurysm formation is common, and ring arrangement of the calcified lesions is inconspicuous.

ARTERIOSCLEROSIS CAUSED BY URANIUM

Aorta.—Lesions of all degrees were found in twenty-three of fifty-two animals which received uranium, alone or together with other substances. If eight animals are excluded, because of the small number of the injections of uranium, there remain twenty-one instances of lesions of the aorta, of all degrees, among forty-four rabbits experimented on, 47.7 per cent. Grossly the aortic lesions present all gradations of severity, from minimal lesions to a profound calcification of the whole vessel. Besides the ordinary calcified plaque commonly observed in spontaneous arteriosclerosis and in experiments with epinephrine hydrochloride, some aortas exhibit a striking annular calcification which I regard as new. The lesions have been classified as severe (+ + in table 1) when the totality or almost the totality of the vessel showed calcification, or when the calcification assumed a distinct annular arrangement; and slight (+ in table 1) when the lesions were few in number, and involved one or at most two regions of the aorta. Reference to the table will show that of twenty-one instances of lesions in the aorta (the numbers with an asterisk always being discarded), ten were "severe." A short description of two of them will suffice.

In rabbit 17, the aorta was dilated and rigid. On the external surface were transverse white hard rings, which gave to the vessel the appearance of a trachea. When the aorta was opened, the calcification was found to be an almost continuous process from the root down. The calcified plates and rings of the wall broke on flattening out the aorta. The elasticity was lost, except at the lumbar portion.

In rabbit 41, the whole of the aorta, from the root down, contained confluent rounded plaques involving the entire circumference of the vessel. Practically the entire aorta was unhealthy.

The remaining eight cases were not as severe as the two just described. A roentgenogram of the aorta of rabbit 49 (fig. 3) showed that the rings extended from the root to the opening of the renal arteries. The ascending arch was dilated and totally calcified. The lesions were least severe in rabbit 3, but the nature of the lesions was such (fig. 2)

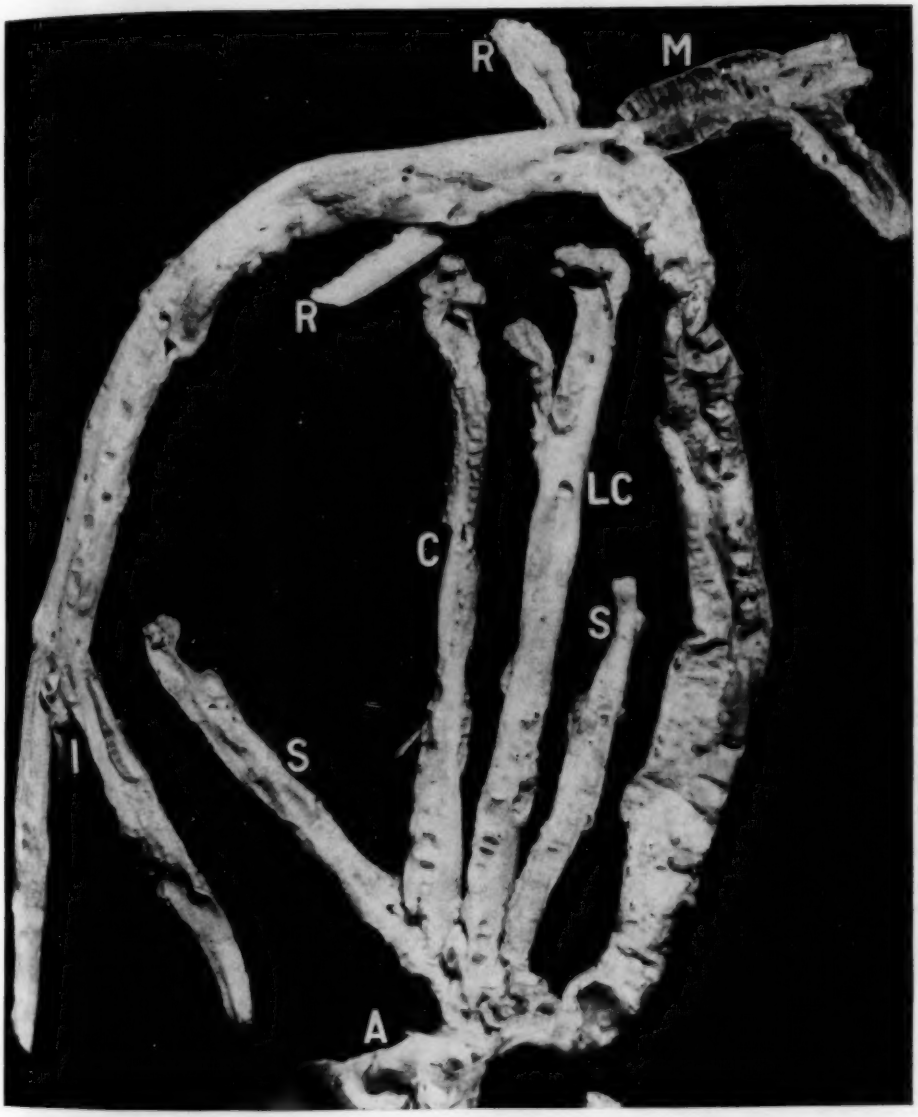

Fig. 1 (rabbit 5).—Aorta and branches; *A* indicates aorta; *C*, carotid; *L C*, left carotid (in the loop during life); *S, S*, subclavian arteries; *M*, superior mesenteric artery; *R, R*, renal arteries, and *I*, iliac arteries. The severe changes in the mesenteric artery and the rings in the mesenteric iliac and subclavian arteries should be observed. The discrete lesions of the renal arteries are not seen in the photograph. The carotid in the loop was less affected than the other one.

that I cannot classify this calcification with anything described before in experimental arteriosclerosis. The thoracic aorta of rabbit 3 was dilated, but free from gross lesions. An approximate idea of the appearance of the aortas in the other cases (rabbits 4, 32, 36, 42 and 46) may be obtained from figure 1 (rabbit 5).

Of the eleven rabbits whose lesions have been called "slight," one (rabbit 27) had a few small plaques at the root and three good-sized plaques at the bifurcation; another (rabbit 37) presented a large plaque

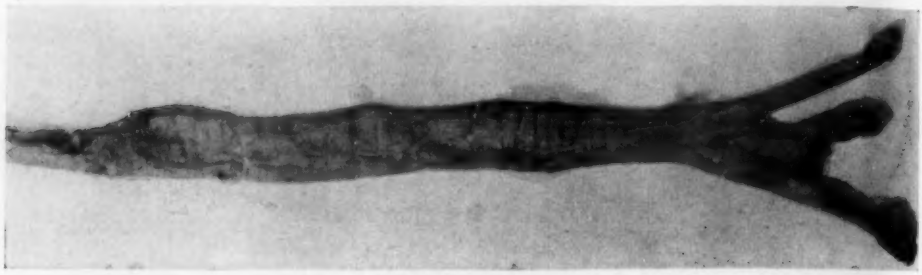

Fig. 2 (rabbit 3).—Lumbar aorta and common iliac arteries. Calcified rings forming hard ridges on intima.

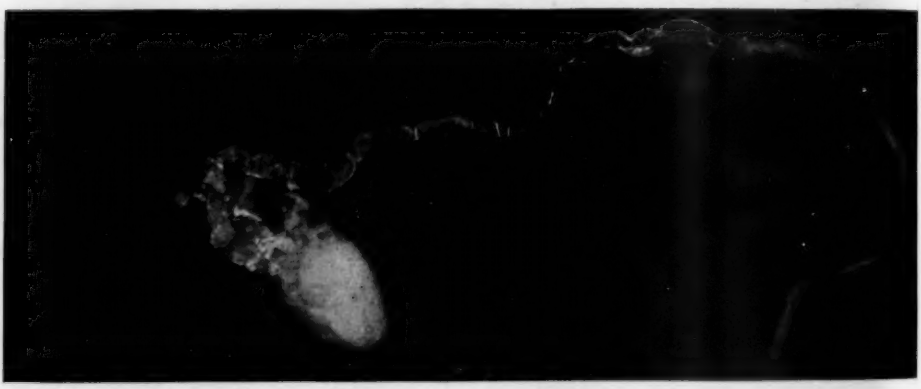

Fig. 3 (rabbit 49).—Roentgenogram (positive). The marked dilatation of the root of the aorta should be noted. Calcified rings are seen as transverse white lines. The process stops at the root of the renal arteries.

on the convexity of the ascending arch, a few small calcified plaques above both coronary cusps and a sharp calcified transverse streak on the ascending arch. The remaining nine (rabbits 7, 13, 16, 22, 24, 25, 29, 44 and 47) exhibited small lesions on the arch, which agreed in extent and description with the so-called spontaneous arteriosclerosis. There has not been any instance of the formation of an aneurysm or of mural thrombosis. Microscopically, the lesions are of only one type:

necrosis and medial calcification, like "spontaneous" sclerosis and sclerosis caused by epinephrine hydrochloride (compare Hesse's [27] observations).

Pulmonary Artery.—Lesions were found in eight animals. In the order of decreasing severity, they were found to be as follows: rabbit 17, several small calcified plaques and two small aneurysms (1 mm. diameter); rabbit 46, many calcified plaques in main trunk; rabbit 3, large saccular aneurysm bulging anteriorly (7 mm. diameter); rabbit 41, three calcified plaques; rabbit 5, two large patches of calcification midway between root and bifurcation; rabbit 44, small plaques at root; rabbits 4 and 36, each, one small patch at bifurcation.

Rings were not present in the pulmonary artery of these animals, but it is noteworthy that two cases of aneurysm should have occurred (rabbits 3 and 17).

Aortic Branches.—The main arteries of the body were affected in fifteen animals. The lesions consisted, as in the case of the aorta, of calcified plaques or calcified rings, and corresponded to a medial calcification resembling Mönckeberg's arteriosclerosis.

I have already stated [28] that the carotid within the loop presents certain lesions (transverse striae) that have been ascribed to the operation itself rather than to the manipulations accompanying the blood pressure measurements. Therefore, in order to avoid ambiguities, all lesions in the carotid loop will be omitted from the present discussion.

The distribution of the lesions in these fifteen animals (exclusive of the loop carotid) is as follows:

TABLE 3.—*Distribution of Lesions in Main Arteries of Body (Exclusive of the Loop Carotid in Fifteen Rabbits*

Location of Lesions	No of Cases	Rabbit Number
All main aortic branches	2	5, 17
All main aortic branches except renal arteries	1	32
Carotid, subclavian, iliac and femoral arteries	2	3, 46
Carotid, renal, iliac and femoral arteries	1	4
Carotid, subclavian and iliac arteries	1	42
Carotid, renal and iliac arteries	1	41, did not have loop
Carotid artery	5	18, 24, 25, 29, 31
Iliac arteries	1	27
Femoral arteries	1	16

In rabbit 17, the lesions assumed the form of rings and not only were present in all the aortic branches but could be followed down the brachial, the femoral arteries, and even the thyroid and parathyroid arteries. The lesions of rabbit 5 may be seen in figure 1. They were

27. Hesse, M.: Virchows Arch. f. path. Anat. **249**:437, 1924.

28. Dominguez (reference 4, second part).

most pronounced in the mesenteric artery. Rings in the iliac arteries (rabbit 3) may be seen in figure 2. Occasionally, the left carotid artery, in situ, shows striations equal to those exhibited by the carotid in the loop, as may be seen in figure 4, in which the vessel on the left represents the loop carotid. For the sake of completeness I may add that in two animals (rabbits 16 and 27) calcified plaques were found in the loop carotid, in addition to the striae, whereas the other carotid was normal. In two other animals (rabbits 18 and 24), on the other hand, plaques were absent in the loop carotid but present in the other one.

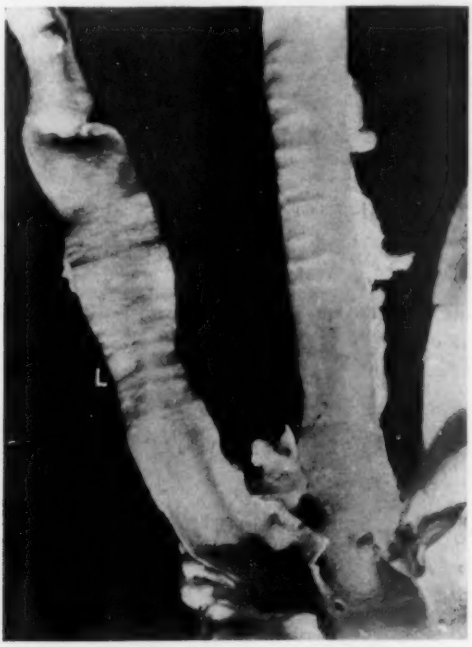

Fig. 4 (rabbit 25).—Carotids. *L* indicates loop carotid. Changes in the other carotid are more marked than is shown in the photograph, but less than those of the loop carotid.

RENAL LESIONS

The lesions in the kidney correspond in the main to those described by Dickson.[29] According to the amount of uranium and the duration of the experiment, various types of anatomic injuries were found, from the large swelling of an acute nephritis (rabbits 1 and 23) to an extraordinary shrinkage of the kidneys with fine granulation of their outer surface (rabbits 27, 28, 29, 31, 37 and 51). The most common

29. Dickson, E. C.: Further Report on Production of Experimental Chronic Nephritis in Animals by Administration of Uranium Nitrate, Arch. Int. Med. **9**: 557 (May) 1912.

lesion found consisted of a reduction of the cortical thickness, with obliteration of the normal striations, fine grayish mottling of the external surface without granulations and an intense congestion of the base of the pyramid. Microscopically, these lesions correspond to a necrotic destruction of the tubules, with and without calcification.

In six animals (rabbits 4, 5, 17, 42, 44 and 46), besides some of the lesions just mentioned, there was a marked calcification, seen with the naked eye as a regular white band at the junction of the outer and middle thirds of the pyramid. On close inspection this band could be resolved into fine streaks along the medullary rays. Microscopically the calcium deposits were found to occur on the limbs of Henle's loops.

Two animals (rabbits 4 and 17) also presented a calcification of the interlobular and afferent arteries, and calcification of the Bowman's

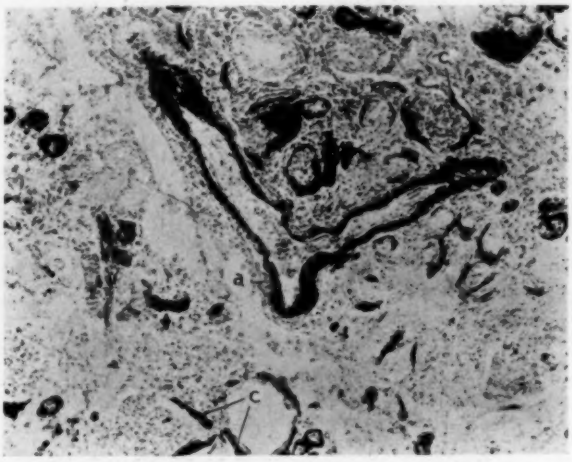

Fig. 5 (rabbit 17).—Photomicrograph of kidney; magnification, × 113.5; frozen section, Van Kossa's stain; *a* indicates artery and *c*, glomerular capsules. Other calcified areas lie in or around tubules.

capsules, to which attention was called previously.[1] These lesions are well illustrated in figures 5, 6 and 7. Rabbit 17 showed, moreover, a marked destruction of the glomeruli, with calcium deposits in the tufts.

GASTRIC LESIONS

The lesions found in the stomach consist in a calcification of the longitudinal muscular coat. Four cases have been recorded (in rabbits 16, 32, 44 and 46), but it must be conceded that, this lesion being entirely unexpected, several cases may have been overlooked before the stomach was systematically examined. The first instance was observed on Oct. 19, 1926 (rabbit 46), and before this day twenty-six of the rabbits in the experiments had already come to autopsy.

The calcification was extensive in three animals (rabbits 32, 44 and 46). A large portion of the anterior and posterior walls of the stomach of these rabbits was covered with white, hard deposits of lime salts, more abundant toward the greater curvature than toward the lesser curvature. These deposits formed streaks and narrow plaques which followed, in a general way, the direction of the longitudinal axis of the stomach. The fundus and pars pylorica were free. In the stomach of rabbit 16 there was only a patch of calcification in the anterior wall of the antrum.

The mucosa was normal in all except rabbit 46. In this animal, the mucosa of the pars pylorica, over the convex border of the organ, and that of the fundus showed several edematous areas, some of which were

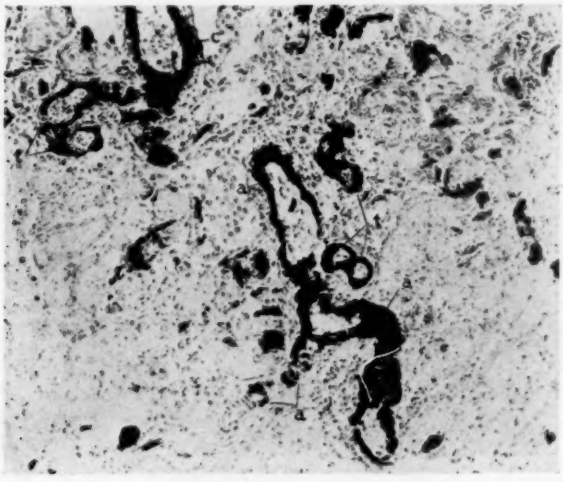

Fig. 6 (rabbit 17).—Another section of kidney; same stain and magnification as in figure 5; *a* indicates artery; *c*, glomerular capsules, and *t*, tubules.

hemorrhagic and were covered with a pseudomembranous exudate. The stomach in this case contained practically no food, but instead about 15 cc. of a milky mucus.

Under the microscope the calcium deposits are found in the outer longitudinal layer of smooth muscle, beneath the serosa. In the immediate neighborhood of these deposits there is fibrosis, hyalinization of connective tissue and a moderate infiltration of mononucleated cells. In decalcified sections the necrosis of smooth muscle is evident. Sections of the hemorrhagic portions of the stomach of rabbit 46 showed the lesion to be in the nature of a hemorrhagic infarction, but an anatomic cause for it was not found. The calcification was localized to the outer muscular coat, and the vessels were intact.

STRIATED MUSCLE

In one animal, rabbit 7, practically all the striated muscles of the body showed calcification. It appeared to the naked eye as long whitish streaks, following the direction of the fibers of the corresponding muscle. The muscles most involved were those of the neck, the serratus major and the abdominal muscles (fig. 8). The diaphragm showed a moderate number of calcified streaks. The muscles of the extremities were the least involved, some appearing normal. Under the microscope (hematoxylin-eosin stain) the lesion appeared as a necrosis of the muscle fiber accompanied by calcification, and with a slight inflammatory reaction. The topography of the muscle was, in general, well preserved. In decalcified sections, the central portion of the lesions had disappeared,

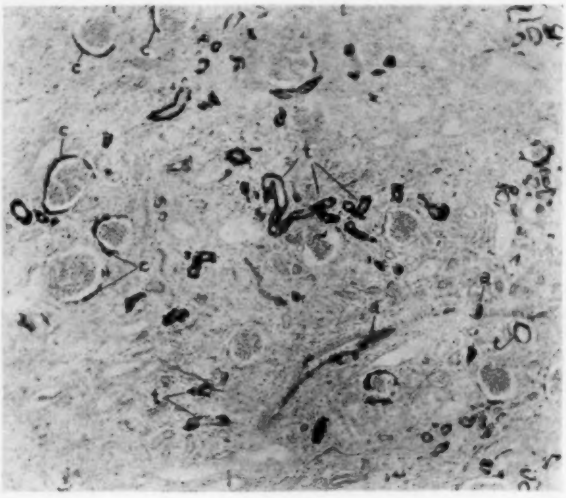

Fig. 7 (rabbit 4).—Photomicrograph of kidney. Frozen section, Van Kossa's stain; *a* indicates artery; *c*, glomerular capsules, and *t*, tubules.

leaving a ragged space bordered by hyaline masses, granular matter and mononucleated cells. At the periphery there was a hyalinized connective tissue with scanty infiltration, in some of the lesions; in others, there was only a slightly thickened connective tissue. As in the case of calcification in the stomach, several of these lesions may have been overlooked before the existence of this muscular injury was recognized. The autopsy of this animal was performed on Oct. 21, 1926, only two days after the first gastric lesion was discovered.

OTHER LESIONS

Osteoporosis has been observed in several animals. It was especially pronounced in rabbits 7 and 44. The ribs of both these animals broke

like cardboard, and the calvarium of the former could be torn away with forceps. Siderosis of the liver was found in several; it was particularly marked in rabbit 36. Finally, there were some of the usual diseases found in rabbits, as coccidial cysts, purulent otitis media and scarred (pitted) kidneys. Some of these are shown in table 1.

COMMENT ON ANATOMIC LESIONS

It is clear from the foregoing experiments that the severe lesions of the aorta cannot be considered as cases of "spontaneous" arteriosclerosis. The "slight" lesions are indistinguishable from the "spontaneous" ones, but since in "spontaneous" arteriosclerosis lesions do not occur in the pulmonary artery and aortic branches, with the possible exception of the iliac arteries (Miles [30]), it is not unreasonable to consider as positive cases caused by uranium such "slight" aortic injuries as were associated with lesions elsewhere in the circulatory system, and also those in which the main arteries were involved, without aortic injury. Selecting the cases on these grounds I obtained nineteen which

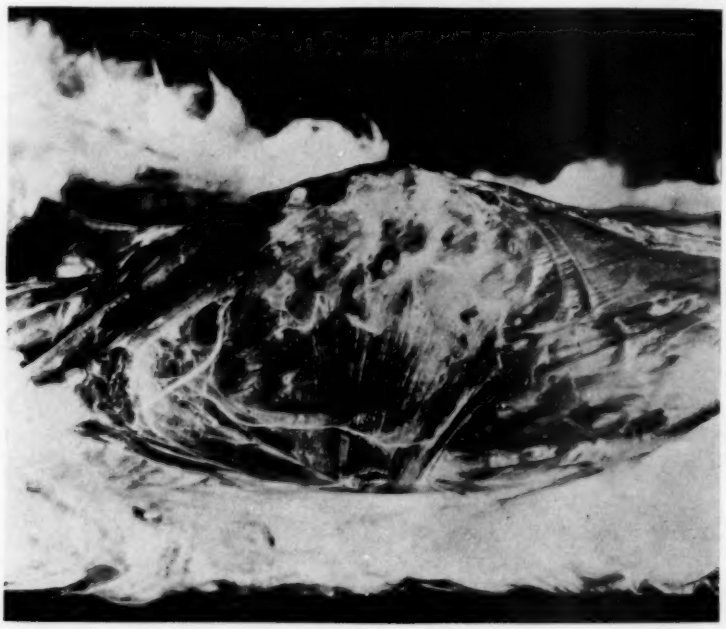

Fig. 8 (rabbit 7).—Right side, head to the left, abdomen upward. The white calcified streaks in the serratus major, abdominal muscles and pectoralis minor should be noted.

30. Miles, A. B.: Spontaneous Arterial Degeneration in Rabbits, J. A. M. A. **49**:1173 (Oct. 5) 1907.

may be regarded as positive arteriosclerosis caused by uranium. The interrelations of the lesions in these nineteen animals are seen in table 4.

There may be some difficulty in accepting case 7 as one of arteriosclerosis caused by uranium. The lesion in the aorta was slight. There was not any other injury to the circulatory apparatus, but a severe one to the striated musculature of the body. The question remains, was this muscular calcification caused by uranium? I do not know that it was caused by uranium any more than I know that the arterial lesions were caused by it. In the arterial lesions, the severity and the

TABLE 4.—*Interrelations of Lesions in Nineteen Animals with Arteriosclerosis Caused by Uranium*

	Location of Lesion			Calcification in			
Rabbit	Aorta	Pulmonary	Arteries	Kidney	Stomach	Musculature	Uranium Sample
3	++	+	+	..	..	..	1
4	++	+	+	+	..	..	1
5	++	+	+	+	..	..	1
17	++	+	+	+	..	..	1
32	++	0	+	..	+	..	2
36	++	+	0	..	..	..	2
41	++	+	+	..	..	..	3
42	++	0	+	+	..	..	3
46	++	+	+	+	+	..	4
49	++	0	0	..	..	..	4
7	+	0	0	..	..	+	1
16	+	0	+	..	+	..	1
24	+	0	+	..	..	..	2
25	+	0	+	..	..	..	2
27	+	0	+	..	..	..	2
29	+	0	+	..	..	..	2
44	+	+	0	+	+	..	3
18	0	0	+	..	..	..	1
31	0	0	+	..	..	..	2
No. of cases 19	17	8	15	6	4	1	

frequency of the lesions warranted the inference of an intimate relationship between the two. Only one case of injury to the striated muscle was observed, but the objection was weakened by the fact that the musculature of the body was not carefully examined in one half of the rabbits, and only when the lesion was so severe that it could not be missed was it recognized. On the other hand, the lesions had everywhere the same pattern, whether they were in the arterial wall, the loops of Henle, the stomach or the striated muscle, namely, necrosis and calcification. I have, therefore, no reason for eliminating this case from the table.

The differences observed in the character and the distribution of the lesions must be looked for in the complex reaction of the animal organism to injury. The following data taken from table 1 will help to

make clear these variations in response: The severe cases of aortic calcification occurred in ten experiments lasting from 76 to 533 days, in which the number of injections varied from nine to seventy-six, and the amount of uranium nitrate from 2.14 to 269 mg. Rabbits 10 and 47 received 452 ± 0.5 mg. in 572 days and were killed while in apparent good health; their aortas were normal. The gross calcification of the kidney was just as erratic. On the other hand, the calcification in the stomach wall appeared more consistently as a late injury in chronic intoxication caused by uranium. In four positive cases (rabbits 16, 32, 44 and 46) the experiments varied in duration from 353 to 535 days, in the number of injections from fifty to seventy-six and in the amount of uranium from 168 to 253.8 mg. The results were similar for the calcification of striated muscle (355 days, forty injections and 151 mg. of uranium).

The question of loss in body weight may be considered now. Of twenty-seven animals which died of intoxication caused by uranium, seventeen showed arteriosclerosis; that is, practically all the positive cases fall in this group. Of these twenty-seven, eighteen lost more than 500 Gm., and among these eighteen, killed, were eleven with arteriosclerosis (seven severe). Of seventeen animals that were killed, only two showed "slight" lesions in the circulatory apparatus (rabbits 18 and 24). Both lost less than 500 Gm. The differences between these two groups of deaths from uranium and the group of animals which were killed are probably real, since both groups compare well in the duration of the experiment and in the amount of uranium given, so that it cannot be said that arteriosclerosis was uncommon or absent among the killed animals because these rabbits received less uranium or because time was not allowed for results to develop. As a matter of fact, the longest experiments were made and the largest amounts of uranium were found among the killed animals (rabbits 10, 33 and 47). Evidently, some rabbits possess a marked resistance toward uranium. Others, to the contrary, exhibit marked susceptibility to it, and in summary of the preceding paragraphs it may be said that among the rabbits which show in their loss of weight and general behavior their intolerance toward uranium, the chances of finding arteriosclerosis are greatest.

Several complicating factors in the nineteen rabbits retained as having positive arteriosclerosis caused by uranium may be discussed now: 1. Operation on the carotid loop: As table 1 shows, in all these nineteen rabbits but one (rabbit 41), a carotid loop had been made. But eighteen other rabbits with carotid loop received uranium and did not show arterial lesions. 2. In rabbit 5 suprarenalectomy had been performed several months before the first dose of uranium was injected.

However, I have examined the aortas and measured the blood pressure of nineteen rabbits on which suprarenalectomy was performed by Dr. Rogoff,[31] and I have not found arteriosclerosis in them. This experiment is instructive, however, in that a severe arteriosclerosis (of the type caused by epinephrine hydrochloride) was developed under the influence of uranium after the main source of epinephrine (the suprarenals) had been removed. 3. The other complicating factors are the mixed intoxications, lead, radium and vanadium, purposely produced (with the exception of rabbit 17), as explained in the introductory remarks. From this point of view, the positive experiments appear as shown in table 5.

The only conclusion to be drawn is that commercial preparations of uranium nitrate are in themselves sufficient to induce arteriosclerosis in the rabbit. Other conclusions as to the predisposing or inhibiting effect of certain metals on arteriosclerosis caused by uranium are made

TABLE 5.—*Results of Positive Experiments*

Substance or Substances Used	Number of Rabbits	Arteriosclerosis	
		Positive	Severe
Uranium alone (all samples)	24	14	7
Uranium and lead	2	2	1
Uranium, lead and radium	4	0	0
Uranium and radium	12	2	1
Uranium and vanadium	2	1	1
	44	19	10

illusory by the great variability in the response of the animals and the small number of the experiments.

It seems to me that here there is a good field for a genetic study of arteriosclerosis. By proper selection and interbreeding along the lines of the already classic work of Maud Slye on the cancer of the rat, it might be possible to throw light on the inheritance of the susceptibility to arteriosclerosis. When one has control of this factor, the experimental study of arteriosclerosis will become less erratic than it is at present.

BLOOD PRESSURE

References to the method used in these experiments for the measurement of the blood pressure are given in the section on "material."

The systolic blood pressure was measured almost daily in thirty-two rabbits. Toward the end of the investigation, however, the measurements were made every four days, as the result had been so consistently negative. It is estimated that the number of blood pressure readings

31. Rogoff, J. M., and Dominguez, R.: J. Metab. Research **6**:141, 1924.

taken in these animals during the intoxication period is approximately 40,000. The results of these observations may be summarized as follows:

1. Changes in blood pressure did not occur under the influence of radium (rabbits 56 and 57), lead (rabbits 60, 61, 62 and 63) or vanadium (rabbit 65). A summary of the clinical history of rabbit 62, with a somewhat detailed account of the blood pressure, has been given previously.[32]

2. Changes in blood pressure did not occur in acute lead poisoning. Rabbit 59 was given 1.7 Gm. of lead acetate by stomach tube in seventeen days. It died two days after the last dose, in convulsions. The blood pressure oscillated between 120 and 140 mm. of mercury during this time.

3. Changes in blood pressure were not found in acute intoxication caused by uranium (rabbits 1 and 23). The control period in these animals was 186 days.

4. Under the influence of injections of uranium the blood pressure, in general, lowered.

Figure 9 illustrates what is meant by a lowering of the blood pressure. Suprarenalectomy had been performed on this animal (rabbit 5) a year before. The part of the graph from Aug. 12, 1924, before suprarenalectomy, to Dec. 4, 1924, nine weeks after the second operation, has been reproduced.[33] The blood pressure of rabbits 7, 9, 16, 18, 20, 46 and 50 behaved similarly to that of rabbit 5.

The blood pressure was low to start with and remained low throughout the experiment in rabbits 8, 25, 28, 33 and 36. In these five animals the blood pressure was rarely higher than 100 mm. of mercury. In rabbits 4, 6 and 37, the pressure lowered soon after the beginning of the intoxication and then slowly recovered its original level (below 120 mm. of mercury) toward the end of the experiment. Rabbit 3 maintained its initial level of pressure (between 130 and 140 mm. of mercury, occasionally higher) during the whole course of the experiment; the pressure sank rather critically below 100 mm. of mercury two days before death. In rabbit 11 the pressure fell when pneumonia developed. No change took place in rabbit 2, the pressure oscillating between 121 and 141 mm. of mercury.

Finally, in rabbits 21 and 22 the blood pressure increased from 90 to 130 mm. of mercury during the lead and radium intoxication, and then lowered as the experiment with uranium began. The twenty-

32. Dominguez (reference 4, second part, "Blood pressure in pathological conditions," rabbit 487).

33. Rogoff and Dominguez (footnote 31, fig. 4, rabbit *D* 65).

one experiments are, then, uniformly consistent, and show that in chronic intoxication caused by uranium—varying within a wide range both in duration and in amount of uranium—the blood pressure either falls or remains about the preintoxication level.

5. There is one outstanding exception to this behavior of the blood pressure (rabbit 17). The graph is given in full (fig. 10). From *A* to *B* the animal was given lead carbonate by mouth. At *B* lead was discontinued, as explained in the introductory remarks and the section on general results. Three months later, on Sept. 3, 1924, the first injection of uranium was given (arrow in graph). From the fifth injection on, the blood pressure oscillated not only at higher levels than ever before, but in the vicinity of physiologic limits.[4] In the last

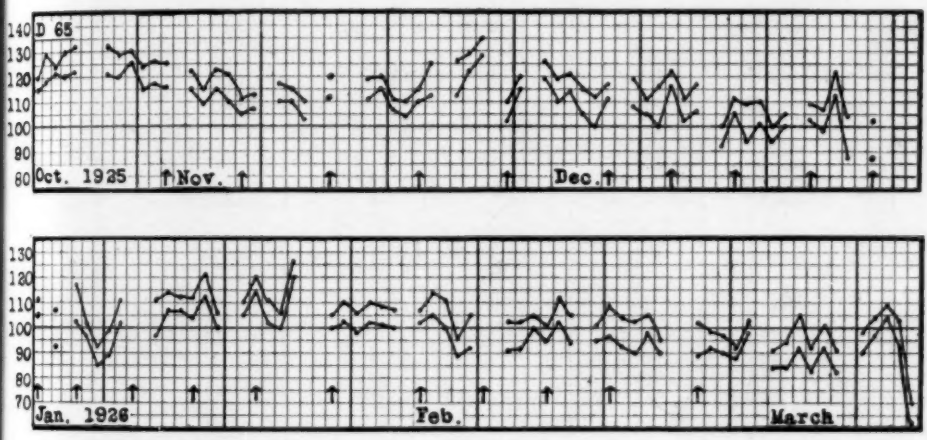

Fig. 9.—Blood pressure curve of rabbit 5. Arrows at bottom represent injections of uranium. The animal died on March 12, during the night. In this and figure 10, the ordinates represent blood pressure, millimeters of mercury; the abscissas, time, days; the upper curve, the highest readings of individual days, the lower curve, the lowest readings; the space between curves, daily oscillation of blood pressure. Daily readings numbered at least 10.

twenty days, when the animal was obviously losing ground, in spite of the cessation of injections of uranium, the pressure was still higher. It must be realized that this was the first experiment performed with uranium, when it was not known that an arteriosclerosis such as was found in this animal could be obtained, and, therefore, that this observation is as unbiased as it is possible to make one. As a matter of fact, all the work reported in the preceding pages was done to duplicate this blood pressure effect, without success.

As previously shown,[28] of ninety normal rabbits the blood pressure of which had been measured for varying periods (including the normal

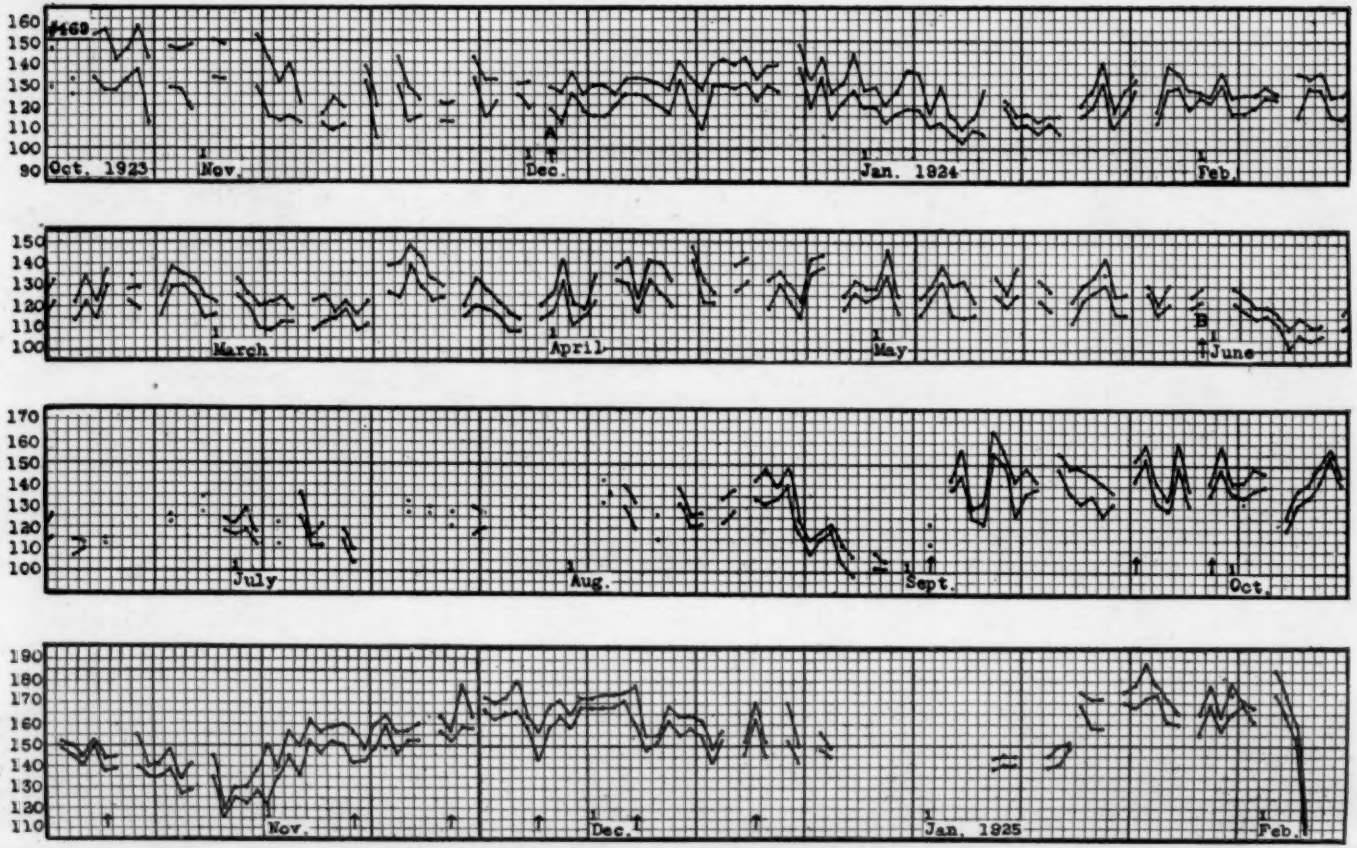

Fig. 10.—Blood pressure curve of rabbit 17; *A* indicates time when lead poisoning was begun; *B*, time when lead poisoning was discontinued; arrows at bottom, from September 3 on, represent injections of uranium. The animal was found dead on February 6.

period of the thirty-two animals of this report), only one (rabbit 489) compares with rabbit 17 under discussion.

The behavior of the pulse rate of this animal in the different periods of the experiment is shown in table 6. As shown in figure 10, period I extends from beginning to *A;* period II from *A* to *B,* that is, during the administration of lead; period III from *B* to the first arrow; period IV from the first arrow to death, that is, during the intoxication caused by uranium. Period V represents the intervals of highest pressures, from November 11 to December 11, and from January 15 to February 3, together. On February 4 and 5, the two days immediately before death, the pulse rate was 240 and 280, respectively.

This case, therefore, satisfies the criterion given previously [28] for a pathologic rise in blood pressure in the rabbit, namely, blood pressure in the neighborhood of 170 mm. of mercury, with a concomitant pulse rate below 200 per minute.

TABLE 6.—*Distribution of Pulse Rate of Rabbit 17 in the Different Periods of the Experiment*

Pulse Rate, Beats per Minute	Number of Counts in Period				
	I	II	III	IV	V
280 to 289	..	..	..	1	..
260 to 279	3	..	..	..	..
240 to 259	8	..	..	1	..
220 to 239	20	1	3	..	..
200 to 219	**24**	11	15	17	2
180 to 199	15	58	17	30	9
160 to 179	10	**80**	9	**55**	**27**
140 to 159	..	21	8	18	7
120 to 139	..	9	2	5	3
	80	180	54	127	48

RELATIONS OF LESIONS TO OBSERVATIONS ON BLOOD PRESSURE

The fact that in intoxication caused by uranium the blood pressure either is unaltered or lowers has the following consequences, when brought into correlation with the anatomic lesions: 1. A severe arteriosclerosis may be produced without any elevation of the blood pressure (rabbits 3, 4, 5, 36 and 46, figs. 1, 2, 3 and 9). 2. A severe arteriosclerosis of the aorta and main arteries is not necessarily accompanied by a high blood pressure. 3. Nephritis of all degrees, from acute swelling down to the stage of granular contraction, caused by uranium, is not accompanied by high blood pressure (twenty-three animals). 4. Slight calcification of the interlobular arteries of the kidney and marked calcification of Bowman's capsules are not necessarily accompanied by a high blood pressure (rabbit 4, fig. 7). 5. The negative effect on the blood pressure is the same, whether the arterial calcification occurs in rings (rabbit 3), in plaques (rabbits 4, 36 and 46) or in both (rabbit 5).

The second consequence does not assume that uranium is responsible for the arteriosclerosis. It would, therefore, remain, even if future work were to deny the part played by uranium in this arterial calcification.

The first and second consequences do not support the mechanical theory of arteriosclerosis.

The exceptional case of rabbit 17 remains for consideration. The lesions in the aorta and main arteries differ from those in the other cases (rabbits 3 and 49, for example) only in degree and extent. The lesions in the kidney differ from those in rabbit 4 in two respects: in the severity of the calcification of the small vessels (figs. 5, 6 and 7 should be compared) and in the glomerular destruction. Many of the glomeruli were completely obliterated, particularly in the outer parts of the cortex, and were the seat of an abundant deposit of calcium. The vessels of the other organs show slight or no change. In certain parts of the heart, the coronary arteries show a discrete calcification involving only a small fraction of the circumference (hematoxylin-eosin preparations). In the thyroid gland, similar discrete changes were seen in sections near the hilum. The spleen and liver were normal. In the brain, many sections from all parts of the organ, especially from the medulla, did not show vascular disease. The organs of this animal had been kept in alcohol to preserve the deposits of calcium, and the brain was examined recently, in view of the report of Bordley and Baker.[34] The facts in this case are, therefore, consistent with the theory that hypertension is intimately connected with injury to the vascular apparatus of the kidney.

LITERATURE ON ARTERIOSCLEROSIS CAUSED BY URANIUM

The only mention I have found in regard to a relation of uranium to arteriosclerosis is the following, from Saltykow's[35] review: "Erwähnt sei hier noch, dass Fischer bei intravenöser Injektion verschiedener Substanzen positive Resultate erhielt, *wenn auch nicht so regelmässig und hochgradig wie bei Adrenalin;* es sind dies: Salzsäure, Phosphorsäure, Milchsäure, phosphorsaurer Kalk, Kaliumbichromat, *Urannitrit,* Chloralamid, Sublimat, Phloridzin, Trypsin, Pepsin, Thyreoidin, Mamma siccata, Kochsalzlösung." (It may be noted, further, that Fischer, on intravenous injection of various substances, obtained positive results, *although not so regularly and not of such a marked character as with epinephrine.* The substances employed were: hydrochloric acid, phosphoric acid, lactic acid, calcium phosphate, potassium bichromate, *uranyl nitrite,* chloralamide, mercuric chloride, phlorizine, trypsin,

34. Bordley, J., and Baker, B. M.: Bull. Johns Hopkins Hosp. **38**:320, 1926.
35. Saltykow (footnote 18, p. 373).

pepsin, iodothyrine, mamma siccata, sodium chloride solution.) (Italics mine.) I regret that I have not read the original work of Fischer. Judging from the phrase in italics, it seems to me that he did not see in his experiments the profound changes I have described here, since these lesions are at least as severe as those produced by epinephrine. My lesions show, besides, some morphologic differences from sclerosis (rings) caused by epinephrine, and are accompanied, furthermore, by frequent involvement of the main arteries of the body.

Dickson [29] did not find any arterial lesions in his experiments on chronic nephritis caused by uranium. He [36] says, "A very striking feature of chronic uranium nephritis is that, even in the advanced cases in which the kidneys are hard and granular, and in which the greater part of the parenchyma is replaced by dense fibrous tissue, there is no demonstrable lesion in the vessels of the kidneys or of the peripheral vascular system." A critical examination of his reports of cases, in the light of table 1, shows the following facts:

Twelve rabbits received an occasional sublethal dose of uranium nitrate. The experiments lasted from thirty-nine to 543 days, the number of injections varied from two to six and the amount of uranium varied from 6 to 25 mg. These experiments do not compare with mine, and some may be discarded, since I have discarded eight of mine in which fewer than eight injections were performed. Four rabbits received from thirty-two to thirty-four injections, and as many milligrams of uranium, in an interval varying from 193 to 457 days. In these four the results may be compared with mine. In only two is the aorta mentioned (rabbits 11 and 14). It was "apparently normal."

Discrepancy is not found, then, between Dickson's negative observations and my positive results.

SUMMARY AND CONCLUSIONS

This paper contains observations on pathologic processes and blood pressure in fifty-two rabbits subjected to intoxication caused by uranium. Some of these animals received lead, radium or vanadium in combination with the uranium or before it was administered. Fourteen additional rabbits served as controls for the administration of the lead, uranium and vanadium. The general results of the investigation are presented in table 1.

Positive results were obtained only in animals which received uranium. The lesions consisted of: (1) arteriosclerosis of the medial calcification type, involving the aorta, pulmonary artery and aortic branches; (2) renal tubular necrosis, with and without calcification of the small vessels and of the Bowman's capsules; (3) necrosis and calcifi-

36. Dickson (footnote 29, p. 584).

cation of the muscular coat of the stomach, and (4) necrosis and calcification of the striated muscles. These lesions are described in detail and then discussed from the standpoint of general response, severity, frequency and mutual relationships.

A section is devoted to the question of "spontaneous" sclerosis and sclerosis caused by epinephrine hydrochloride.

The blood pressure was studied in thirty-two rabbits by means of the van Leersum method (about 40,000 blood pressure readings). Five photographs of anatomic lesions, three photomicrographs of the renal lesions and two blood pressure curves (three graphs) are given.

The following conclusions are reached:

1. Changes in blood pressure do not occur in intoxication caused by radium, lead and vanadium.

2. Acute lead poisoning is not accompanied by a rise in blood pressure.

3. Changes in blood pressure are not observed in acute intoxication caused by uranium.

4. The blood pressure in chronic intoxication with uranium becomes lower or, in general, remains unaltered.

5. Nephritis of all degrees, from acute swelling (conclusion 3) to granular contraction, caused by uranium, is not accompanied by high blood pressure.

6. A severe arteriosclerosis (medial calcification type) of the aorta and main arteries may develop without any elevation of the blood pressure.

7. Conversely, severe arteriosclerosis of the aorta and main arteries is not necessarily accompanied by a high blood pressure. Similar conclusions have been reached in experimental atherosclerosis (intimal fatty deposit).[37]

8. These experiments do not support the mechanical theory of arteriosclerosis.

9. Calcification of Bowman's capsules, with slight calcification of the small vessels of the kidney, is not necessarily followed by a rise in blood pressure.

10. One animal, in which the calcification of the small vessels of the kidney and the glomerular destruction were pronounced, developed a pathologically high blood pressure.

11. The results obtained agree with the idea of an intimate relationship between the vascular apparatus of the kidney and high blood pressure.

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37. Dominguez, R.: J. Exper. Med. **46**:463, 1927.

ALCOHOL IN THE HUMAN BODY*

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This paper, the second of a series on the subject,[1] consists of a report of seventy-five cases, a practical method of determining alcohol quantitatively in cadaveric material, a review of the literature on the subject and conclusions.

It is the established practice in this laboratory when human organs are submitted for analysis to take a 100 Gm. sample of each organ (stomach, kidney, liver, etc.), chop it fine in a meat-chopper, make it acid with tartaric acid and distill it in a current of steam until 100 cc. of distillate is recovered. The distillate is then tested for volatile poisons, including ethyl alcohol. Tests show that all the alcohol is contained in the first 100 cc. of distillate. If alcohol is detected by the iodoform reaction, the distillate is weighed in a pyknometer, and the percentage of alcohol calculated from the specific gravity. Obviously, organic substances other than alcohol might be carried over by steam distillation and affect the specific gravity; therefore the following practice was adopted: 50 cc. of the distillate which gives the iodoform reaction is treated with 5 cc. of a 10 per cent solution of sodium hydroxide and 3 cc. of a 10 per cent solution of silver nitrate to oxidize the volatile aldehydes, to saponify any of the fats and also to fix the fatty acids present. The mixture is distilled, the distillate again weighed in a pyknometer and the precentage of alcohol calculated. This gives a value sometimes higher and sometimes lower than that obtained before purification, owing to the removal of different substances in different cases, and also owing to the difficulty of detecting such small differences in specific gravity. It is evident that the specific gravity method is inaccurate for such small quantities of alcohol as are usually distilled from cadaveric material.

PRACTICAL METHOD OF DETERMINING ALCOHOL IN CADAVERIC MATERIAL

Work on the problem was begun, therefore, about a year ago, with the idea of developing a method which would be applicable to the routine of a toxicologic laboratory. The literature was thoroughly reviewed,

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* From the Chemical Laboratory, Cook County Coroner's Office.

1. McNally, W. D.; Embree, H. C., and Rust, C. A.: J. Biol. Chem. 74:219, 1927.

and some of the recorded methods of obtaining alcohol from animal tissue which seemed to have possibilities were tried out. Among these, two methods were selected for further examination. The method of steam distillation long in use in this laboratory and described previously was tried first, and then the method of Nicloux,[2] which is as follows: 10 Gm. of tissue chopped fine or blood is placed in a 300 cc. Kjeldahl flask and 65 cc. of saturated trinitrophenol solution is added. The trinitrophenol precipitates most of the proteins and prevents frothing. Distillation is carried out at 50 C. under reduced pressure. The tube of the condenser is placed in a small flask which contains enough distilled water to cover the tip of the tube. The receiving flask is immersed in an ice bath. All the measurable alcohol is found in the first 10 cc. of distillate. For determining the quantity of alcohol in the distillate the Nicloux[3] method of titrating with dichromate was chosen after most of the methods recorded in the literature were tried out. This method, as modified and used in this laboratory, is fully described in our first paper. All work was carried out on samples of human organs which had been submitted to this laboratory for toxicologic examination. Table 1 is a report of twenty-five cases in which the specific gravity method of determining the quantity of alcohol was checked against the dichromate titration method. The tests were made on samples of the

TABLE 1.—*Specific Gravity vs. Dichromate Titration* *

	Percentage of Alcohol by the Dichromate Titration Method			Percentage of Alcohol by the Specific Gravity Method		
Case	Stomach	Kidney	Liver	Stomach	Kidney	Liver
1	0.91	0.82	0.80	0.48	0.75	0.32
2	0.45	0.44	0.40	0.62	0.34	0.28
3	0.47	0.50	0.50	0.07	0.27	0.28
4	0.50	0.44	0.39	0.28	0.30	0.35
5	0.72	0.53	0.53	0.77	0.62	0.27
6	0.48	0.44	0.42	0.45	0.21	0.19
7	0.04	0.10	0.08	0.00	0.04	0.00
8	0.88	1.01	0.63	1.05	0.95	0.35
9	0.82	0.76	0.73	0.52	0.62	0.29
10	0.78	0.76	0.78	0.84	0.84	0.57
11	0.42	0.45	0.43	0.21	0.14	0.25
12	1.47	0.58	0.57	0.80	0.18	0.00
13	0.15	0.13	0.15	0.55	0.62	0.51
14	0.48	0.44	0.50	0.00	0.16	0.22
15	2.65	0.68	0.57	1.20	0.77	0.60
16	1.39	0.66	0.52	1.27	0.45	0.17
17	0.47	0.44	0.44	0.84	0.06	0.52
18	1.07	0.78	0.76	0.29	1.26	0.44
19	0.53	0.50	0.52	1.15	0.18	0.37
20	0.79	0.76	0.77	0.22	0.80	0.08
21	0.35	0.38	0.37	0.56	0.62	0.25
22	1.20	0.79	0.69	0.75	0.70	0.42
23	0.97	0.95	0.96	0.00	0.76	0.28
24	0.45	0.47	0.45	0.28	1.20	0.52
25	0.32	0.35	0.34	0.30	0.00	0.44

* Results in cubic centimeters of absolute ethyl alcohol.

2. Nicloux, M.: J. d. physiol. et path. gén. **48**:841, 1896; **57**:652, 1904.
3. Nicloux, M.: Compt. rend. Soc. de biol. **52**:295 and 620, 1900.

steam distillate obtained in the routine analysis of cases. The specific gravity method showed such a wide variation between organs of a given person as to cause doubt of its accuracy, because, as is shown in part 3 of this paper, the different organs of a person contain approximately equal quantities of alcohol at a given time. The results from the dichromate method yielded much more consistent figures. The fact that the stomach generally showed a higher concentration of alcohol than the other organs might be accounted for by assuming that the alcohol had not been completely absorbed at the time of death. The results of these tests led to the adoption of the dichromate method for the quantitative determination of alcohol in this laboratory.

The necessity of purifying the steam distillate by redistilling it with silver nitrate and sodium hydroxide, as described previously, was tried

TABLE 2.—*First Steam Distillate vs. Purified Distillate* *

Case	Percentage of Alcohol in First Steam Distillate	Percentage of Alcohol in Purified Distillate	Case	Percentage of Alcohol in First Steam Distillate	Percentage of Alcohol in Purified Distillate
26	0.45	0.44	39	0.39	0.38
27	0.50	0.49	40	0.40	0.42
28	0.53	0.52	41	0.03	0.03
29	0.72	0.76	42	0.82	0.78
30	0.32	0.30	43	0.21	0.25
31	0.48	0.48	44	0.42	0.39
32	0.44	0.50	45	2.87	2.77
33	0.33	0.34	46	0.04	0.04
34	0.44	0.44	47	0.14	0.14
35	0.53	0.48	48	0.53	0.48
36	0.01	0.01	49	1.47	1.32
37	0.69	0.67	50	0.50	0.50
38	0.09	0.09			

* Results in cubic centimeters of absolute ethyl alcohol in stomach tissue. Nicloux titration method used for evaluation of ethyl alcohol.

out. The results, as shown in table 2, indicate that such purification is unnecessary when the dichromate method is used. This is probably due to the fact that no substances other than alcohol are carried over by steam which will reduce dichromate. The latter supposition was strengthened by tests of the steam distillate of several nonalcoholic samples with dichromate in which reduction of the dichromate was not obtained.

Table 3 shows the results of comparing the method of steam distillation with the method of distilling at reduced temperature and pressure in the presence of trinitrophenol. The regular steam distillate was titrated with dichromate, and a fresh 10 Gm. sample of the same organ was distilled under reduced pressure, as described previously, and titrated with dichromate. The results indicate that the two methods of securing the alcohol from cadaveric material are about equally effective. This laboratory uses the steam distillation method, because the steam distillate is readily available, having been produced for the general tests for volatile poisons. If the iodoform test for alcohol is positive in the

steam distillate, a sample is titrated with dichromate. This method is as accurate as any on record, and is so simple and rapid as to make it well adapted to routine work. It is not interfered with by any of the other volatile poisons which may be present, with the exception of wood alcohol and formaldehyde; neither is it interfered with materially by the organic substances which are present in the steam distillate from animal matter.

TABLE 3.—*Steam Distillation vs. Vacuum Distillation* *

Case	Percentage of Alcohol by Volume in		Case	Percentage of Alcohol by Volume in	
	Steam Distillate	Vacuum Distillate		Steam Distillate	Vacuum Distillate
51	0.03	0.06	64	0.48	0.44
52	0.44	0.44	65	0.04	0.04
53	0.49	0.48	66	0.03	0.05
54	0.53	0.50	67	0.40	0.38
55	0.72	0.71	68	0.50	0.48
56	0.32	0.30	69	0.40	0.44
57	0.48	0.50	70	0.01	0.03
58	0.03	0.06	71	0.35	0.37
59	0.09	0.08	72	0.08	0.09
60	0.03	0.05	73	0.19	0.19
61	0.44	0.40	74	0.63	0.62
62	0.50	0.48	75	0.40	0.44
63	0.44	0.40			

* Nicloux method, a stomach tissue being used.

REPORT OF SEVENTY-FIVE CASES

Every specimen submitted to this laboratory for analysis, beginning Feb. 21, 1927, which was either diagnosed as alcoholic or subsequently found to be alcoholic, was subjected to the following procedure: The steam distillate secured in the usual way, as described previously, was tested for alcohol qualitatively by the iodoform reaction, and quantitatively by the specific gravity and the dichromate methods. It was then treated with sodium hydroxide and silver nitrate, as described previously, redistilled and the distillate again quantitated by specific gravity and by titrating with dichromate. A fresh 10 Gm. sample was ground up and distilled with trinitrophenol under reduced pressure, as described, and the distillate quantitated by specific gravity and by dichromate. The results are tabulated in tables 1 to 5. Tables 1, 2 and 3 contain data pertaining to the method and have been discussed in part 1. Table 4 gives the percentage of alcohol found in the stomach, kidney and liver in seventy-five cases. It will be noted that the quantities in the three organs of a given patient were about parallel, the quantity in the stomach generally being a little higher than that in the other two organs. When large quantities of alcohol were present, as in cases 41 and 49, the quantity in the stomach was much higher than that in the other organs, death probably having occurred before absorption was complete.

Table 5 contains a brief history of the patient, when such was obtainable, the preliminary diagnosis, the quantity of alcohol found and the final verdict of the coroner. This was probably the most important information supplied by the investigation. It showed the importance of making a chemical analysis before a final verdict was rendered. An examination of table 5 shows several cases, such as 8 and 9, which were diagnosed as being alcoholic but were proved not to be by chemical analysis. In other cases, as 32 and 46, the diagnosis was something other than alcoholism, but chemical analysis proved that they were alcoholic.

REVIEW OF THE LITERATURE

From the results published in our first paper it is evident that small quantities (less than 0.01 per cent) of ethyl alcohol are normally present in the tissue of the placenta of the human body. We will now quote the results of other workers on tissues of human beings and of animals, first, to corroborate our own results and second, to furnish grounds for the conclusions drawn.

TABLE 4.—*Percentage of Alcohol by Volume in Seventy-Five Cases*

Case	Stomach	Kidney	Liver	Case	Stomach	Kidney	Liver
1	0.02	0.02	0.02	39	0.01	0.01	0.01
2	0.36	0.35	0.32	40	0.33	0.36	0.34
3	0.40	0.40	0.40	41	2.28	1.17	0.86
4	0.42	0.35	0.31	42	0.97	0.40	0.38
5	0.00	0.00	0.00	43	0.00	0.00	0.00
6	0.57	0.42	0.40	44	0.02	0.02	0.01
7	0.32	0.30	0.30	45	0.30	0.03	0.07
8	0.00	0.00	0.00	46	0.12	0.10	0.12
9	0.00	0.00	0.00	47	0.40	0.40	0.40
10	0.38	0.36	0.33	48	1.30	0.54	0.45
11	0.08	0.08	0.06	49	2.10	0.61	0.54
12	0.01	0.01	0.01	50	0.95	0.68	0.40
13	0.07	0.07	0.05	51	0.76	0.43	0.42
14	0.70	0.57	0.51	52	1.10	0.52	0.28
15	0.08	0.06	0.06	53	0.27	0.22	0.21
16	0.30	0.25	0.21	54	0.03	0.01	0.01
17	0.00	0.00	0.00	55	0.00	0.00	0.00
18	0.00	0.00	0.00	56	0.22	0.03	0.02
19	0.85	0.65	0.56	57	0.01	0.00	0.00
20	0.22	0.21	0.20	58	0.22	0.20	0.15
21	0.05	0.05	0.03	59	0.15	0.00	0.00
22	0.07	0.04	0.06	60	0.28	0.30	0.23
23	0.00	0.00	0.00	61	1.18	0.04	0.03
24	0.22	0.20	0.21	62	0.02	0.01	0.01
25	0.00	0.00	0.00	63	0.04	0.10	0.07
26	0.02	0.02	0.03	64	0.17	0.16	0.13
27	0.05	0.05	0.03	65	0.70	0.47	0.45
28	0.00	0.00	0.00	66	0.90	0.78	0.72
29	0.05	0.05	0.06	67	0.11	0.22	0.12
30	0.01	0.01	0.01	68	0.47	0.40	0.40
31	0.65	0.22	0.25	69	0.00	0.00	0.00
32	1.12	0.81	0.62	70	0.22	0.20	0.21
33	0.00	0.00	0.00	71	0.89	0.82	0.64
34	0.17	0.14	0.11	72	0.20	0.18	0.19
35	0.00	0.00	0.00	73	1.67	0.66	0.45
36	0.00	0.00	0.00	74	0.46	....	0.15
37	0.00	0.00	0.00	75	0.14	0.28	0.11
38	0.00	0.00	0.00				

Ford [4] found that fresh ox blood contained 0.0009 per cent of alcohol. Bodlander [5] showed that about 95 per cent of the alcohol taken into the body is oxidized to carbon dioxide and water, and that the remainder is eliminated through the kidneys and lungs, and a small quantity through the skin. Grehant worked on the problem for twenty years, and published a series of some fifteen papers.[6] His experiments indicated the

4. Ford, W. H.: New York M. J. **15**:562, 1872.

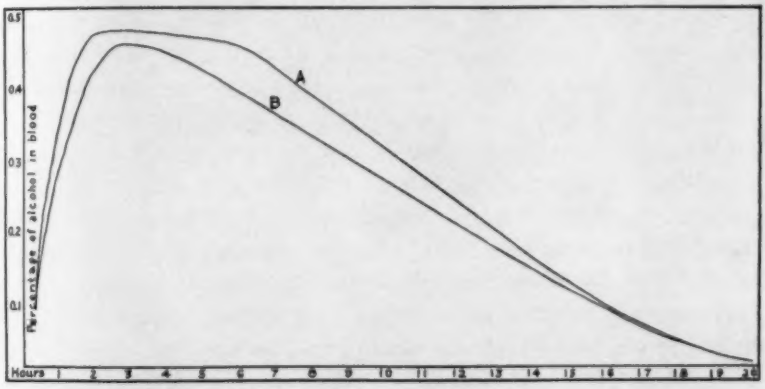
5. Bodlander, G.: Pflüger's Arch. f. d. ges. Physiol. **11**:122, 1875.

6. Grehant: Compt. rend. Acad. de sc. **120**:1154, 1895; **123**:192, 1896; **129**: 746, 1899; Compt. rend. Soc. de biol. **48**:839, 1896; **51**:808 and 946, 1899; **52**: 894, 1900; **55**:225, 376, 802 and 1264, 1903; J. de physiol. et path. gén. **9**:879, 1907.

TABLE 5.—*Summary of Observations in Cases Studied*

Case	History	Diagnosis	Percentage of Alcohol by Volume	Verdict
1	Died suddenly	Alcoholism	0.01	Heart failure
2	Found dead in street	Alcoholism	0.35	Acute alcoholism
3	Found dead in bed	Alcoholism	0.40	Acute alcoholism
4	Found dead in street	Alcoholism	0.36	Acute alcoholism
5	Found in coma	Alcoholism	0.00	Heart failure
6	Found dead in alley	Alcoholism	0.47	Acute alcoholism
7	Found dead in alley	Alcoholism	0.30	Acute alcoholism
8	Found dead in bathtub	Alcoholism	0.00	Cause unknown
9	Sick two hours; vomiting	Alcoholism	0.00	Heart failure
10	Found dead in alley	Alcoholism	0.36	Acute alcoholism
11	Strangled in a fight	Suffocation	0.08	Acute alcoholism
12	Sudden death	Alcoholism	0.01	Cause unknown
13	Strong drinker	Alcoholism	0.07	Chronic alcoholism
14	Found dead	Alcoholism	0.60	Acute alcoholism
15	Worked in lead factory	Lead poisoning	0.07	Chronic lead poisoning
16	Found in coma	Alcoholism	0.26	Acute alcoholism
17	Took barbital	Barbital poisoning	0.00	Acute hemorrhage
18	Took nitric acid	Acid poisoning	0.00	Nitric acid poisoning
19	Found dead	Alcoholism	0.70	Acute alcoholism
20	Swallowed incense	Poisoned	0.21	Chronic alcoholism
21	Found dead in barn	Alcoholism	0.05	Chronic alcoholism
22	No history	.....	0.05	Persistent thymus
23	Was given neo-arsphenamine	Alcoholism	0.00	Arsenical poisoning
24	No history	Gas	0.21	Acute alcoholism
25	Found dead	Alcoholism	0.00	Chronic myocarditis
26	Found dead in hallway	Alcoholism	0.02	Gas
27	Sick 36 hours; coma	.....	0.04	Chronic alcoholism
28	Found dead in hotel	Alcoholism	....	Heart failure
29	Died in coma	Alcoholism	0.05	Influenza
30	No history	.....	0.01	Acute alcoholism
31	Skull fracture	Alcoholism	0.30	Skull fracture
32	Found dead in bed	Heart failure	0.85	Acute alcoholism
33	No history	Alcoholism	0.00	Heart failure
34	Broken nose	Alcoholism	0.14	Shock and hemorrhage
35	No history	Alcoholism	0.00	Heart failure
36	Found dead	Alcoholism	0.00	Starvation
37	Found dead	Alcoholism	0.00	Undetermined
38	Sick one day	Alcoholism	0.00	Heart failure
39	Died suddenly	Alcoholism	0.01	Heart failure
40	Found dead	Alcoholism	0.35	Acute alcoholism
41	Found dead in street	Alcoholism	1.30	Acute alcoholism
42	No history	Alcoholism	0.65	Acute alcoholism
43	Died suddenly	Alcoholism	0.00	Mercury poisoning
44	No history	Gas	0.02	Undetermined
45	Found dead	Alcoholism	0.13	Chronic alcoholism
46	Died suddenly	Heart failure	0.12	Chronic alcoholism
47	Hit by automobile	Alcoholism	0.40	Shock and hemorrhage
48	Found dead	.....	1.10	Acute alcoholism
49	Found dead in alley	Alcoholism	1.80	Acute alcoholism
50	Strangled in a fight	Alcoholism	0.66	Strangulation
51	Died in cell at police station	Alcoholism	0.53	Acute alcoholism
52	Found dead	Heart failure	0.60	Acute alcoholism
53	Rib fracture	Alcoholism	0.25	Gas
54	Found in coma	Alcoholism	0.01	Heart failure
55	Ate tainted food	Ptomaine	0.50	Acute alcoholism
56	Opium eater	Opium poisoning	0.09	Chronic alcoholism
57	No history	Alcoholism	0.00	Injury
58	Had been drinking	Alcoholism	0.20	Shock and hemorrhage
59	Found dead	Alcoholism	0.05	Heart failure
60	Dropped dead	Heart failure	0.27	Acute gastritis
61	Found dead	Alcoholism	0.42	Alcoholism
62	Ill one day	.....	0.02	Chronic alcoholism
63	Found dead in bathroom	Alcoholism	0.07	Chronic alcoholism
64	Found dead	Alcoholism	0.16	Shock and hemorrhage
65	Found dead	Alcoholism	0.54	Alcoholism
66	Found dead	Alcoholism	0.80	Acute alcoholism
67	No history	.....	0.15	Chronic alcoholism
68	Was given poison	Poisoned	0.43	Acute alcoholism
69	No history	Alcoholism	0.00	Cause unknown
70	No history	Alcoholism	0.21	Acute alcoholism
71	No history	Alcoholism	0.70	Acute alcoholism
72	No history	Alcoholism	0.19	Acute alcoholism
73	Found dead	Alcoholism	0.98	Acute alcoholism
74	Took barbital	Barbital poisoning	0.30	Acute alcoholism
75	Died suddenly	Alcoholism	0.20	Acute alcoholism

following facts: When alcohol is introduced into the body, either by stomach or by injection into the blood stream, the method used does not make any difference; it passes rapidly to all the tissues and fluids of the body by diffusion. Within an hour and a half, 90 per cent of the alcohol will thus have been absorbed. If the blood, urine or tissues is analyzed between two and four hours after the alcohol is taken and the percentage of alcohol is multiplied by the body weight, the result will show approximately the total quantity of alcohol taken. Elimination of the alcohol by oxidation begins soon after it is absorbed and proceeds slowly for the first four to six hours, after which it is more rapid, elimination being complete in twenty-four hours, with large quantities of alcohol, and somewhat sooner with smaller quantities. This rate of absorption and elimination is rather uniform in different persons and



Absorption and elimination of alcohol when 5 Gm. per kilogram of body weight has been taken. *A* indicates the curve of the person unaccustomed to alcohol; *B*, that of the person accustomed to alcohol.

is represented by a curve in the chart (Pringsheim). If a person is accustomed to alcohol, elimination starts a little more promptly and proceeds a little more rapidly, as indicated in the chart. The plateau of maximum concentration represents the period of drunkenness. The person shows signs of being affected when 0.2 Gm. of alcohol per kilogram of body weight is taken, whereas the taking of 0.5 Gm. causes a condition of drunkenness and from 0.8 to 1.0 Gm. will cause death. Maurice Nicloux[7] published papers on the subject from 1896 to 1913. He found that the blood of a normal dog contained 0.0018 per cent of alcohol. All his work with administered alcohol tended to corroborate

7. Nicloux, M.: Compt. rend. Soc. de biol. **48**:841, 1896; **52**:295 and 620, 1900; **54**:754, 1902; **57**:652, 1904; **60**:1034, 1906; **61**:492, 1906; **73**:59 and 177, 1912; **74**:267, 1913.

the results of Grehant. Maignon [8] found from 0.0015 to 0.0031 per cent of alcohol normally present in dogs. Pringsheim [9] reported from 0.0023 to 0.0044 per cent normally present in rats. Schumm [10] reported that the amounts of alcohol in the blood and spinal fluid were nearly identical. Schweisheimer [11] found that normal human blood contained from 0.0030 to 0.0037 per cent of alcohol. He also tested animals which had been fed alcohol and constructed curves for the absorption and elimination of alcohol which were identical with those of Grehant and Nicloux. Voltz and Dietrich [12] found from 0.0023 to 0.0030 per cent of alcohol normally present in dogs. Mellanby [13] drew the following conclusions from the experiments which he carried out. Intoxication is related to the amount of alcohol in the blood. Dilute solutions of alcohol are less intoxicating than strong solutions containing the same amount of alcohol. Food inhibits intoxication. Alcohol can supply from 30 to 40 per cent of the total energy lost by the body but it cannot supply muscular energy. It can supply heat energy and leave the other foodstuffs to supply the muscular energy. Alcohol in high concentrations inhibits its own oxidation. Kuhn [14] found an average of 0.0021 per cent of alcohol in the blood of normal human beings.

Landsburg [15] reports from 0.0028 to 0.0083 per cent in the muscle of rabbits. Southgate [16] made comparative tests of the alcoholic content of blood and urine in men who had taken a known amount of alcohol. He found that the percentage of alcohol ran parallel in the blood and the urine except that the urine was a little higher in alcoholic content from one to six hours after the alcohol had been taken. Aoki [17] found from 0.002 to 0.003 per cent of alcohol in the blood of rabbits, 0.0025 per cent in the blood of fowls and 0.0035 per cent in the livers of fowls. Gettler [18] reported from 0.0006 to 0.0023 per cent of alcohol in the brains of normal human beings. McNally, Embree and Rust found from 0.0009 to 0.0052 per cent of alcohol in the tissue of the placenta.

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8. Maignon, F.: Compt. rend. Acad. d. sc. **140**:1064, 1905.
9. Pringsheim: J. Biochem. **12**:142, 1908.
10. Schumm, O.: Deutsche Ztschr. f. Nervenh. **46**:275, 1913.
11. Schweisheimer, W.: Deutsches Arch. f. klin. Med. **109**:271, 1912.
12. Voltz, W., and Dietrich, W.: Biochem. Ztschr. **68**:118, 1915.
13. Mellanby, E.: Med. Research Commission, London, 1919, special report, no. 31.
14. Kuhn, G.: Arch. f. exper. Path. u. Pharmakol. **103**:295, 1924.
15. Landsburg, G.: Ztschr. f. physiol. Chem. **41**:505, 1924.
16. Southgate, H. W.: Biochem. J. **18**:101, 1924; Brit. M. J. **1**:463, 1926.
17. Aoki, M. J.: J. Biochem. **5**:329, 1925; **6**:307, 1926.
18. Gettler, A. O., and Tiber, A.: Arch. Path. **3**:75 and 218 (Jan. and Feb.) 1927.

SUMMARY

From the work recorded in the literature and from our experience in analyzing cases of alcoholism, we have arrived at the following conclusions: When alcohol is taken into the body it is rapidly absorbed and passes to all fluids and tissues of the body in approximately equal amount, so that within an hour and a half it is practically all absorbed and an analysis of the blood, urine or tissue will give a fairly accurate measure of the alcohol present. The alcohol is usually eliminated from the body within twenty-four hours. The human body normally contains about 0.003 per cent of alcohol. A chemical analysis of fluids or tissue of the body showing alcohol to be present in excess of 0.01 per cent indicates that alcohol has been taken recently. If such analysis is made from two to six hours after the taking of alcohol and the result is multiplied by the body weight, it will give approximately the total quantity of alcohol taken. The presence of from 0.4 to 0.5 per cent of alcohol represents a condition of drunkenness, and for a man of average weight means that about 300 Gm. of alcohol has been taken. This amount would be present in about a pint of ordinary whisky. Twice this amount, or from 0.8 to 1 per cent, of alcohol in the body will cause death.

THE DIFFERENTIAL BLOOD COUNT OF THE NORMAL GUINEA-PIG

A STATISTICAL STUDY, WITH OBSERVATIONS ON THE NATURE OF THE KURLOFF BODY *

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While attempting to determine the normal differential blood count of a group of guinea-pigs, which were to be used for experimental purposes, one of us (S. P. L.) [1] noted and reported that the resulting percentage distributions of cell types did not agree with those reported by previous investigators. A search of the literature brought to light marked variations in counts taken from so-called normal guinea-pigs. Accordingly, the following study of cell types was undertaken, and a large series of counts was made in an attempt to establish criteria of normality for the differential count of the blood of the guinea-pig.

METHOD OF PROCEDURE

A group of forty-two healthy adult guinea-pigs was selected at random from a herd of previously unused and apparently normal animals. Both males and females were included in the study, but gravid females were excluded and the individual animals isolated during the experiment. During one year, 303 counts were made from forty-two guinea-pigs [2]; the weight was recorded every time an animal was bled in order to eliminate any showing excessive loss.

Preparations.—The ear of a guinea-pig was shaved with the least possible amount of irritation. The animal was allowed to wait for half an hour, after which the ear was bathed in warm water, cleansed with alcohol and air dried. Blood was obtained from the marginal ear vein by stabbing with a 24 *G* hypo dermic needle which had been previously washed and stored in alcohol. Smears were made on slides by pushing the end of one slide along the surface of a second on which a drop of blood had been placed. This caused the blood film to spread along the surface of the slide. The smears were usually stained with a fresh solution of Wright's stain. Giemsa's stain was sometimes used because with it differentiation of cell types was more easily studied. When it became difficult to differentiate between cells of the lymphocytic and leukocytic series, the oxidase

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* From the George William Hooper Foundation for Medical Research, University of California, San Francisco, and the Department of Hygiene, University of California, Berkeley.

1. Lucia, S. P.: Proc. Soc. Exper. Biol. & Med. **24**:132, 1926.

2. Protocols of the original data may be obtained from the office of the Department of Hygiene, University of California, on request.

method of staining was used.[3] This method makes use of the fact that the granules of the leukocytes stain brown in the presence of benzidine, producing a difference in appearance between them and the lymphocytes.

In addition to this procedure, coverslip preparations were made simultaneously, the supravital technic of Rosin and Bibergeil, as described by von Domarus,[4] being used. This method, which depends on the fact that living cells are stained more slowly than dead cells by certain dilute nontoxic solutions of dye, is designed to make possible observations of the behavior of living cells. These preparations were found to be useless for counting, since this technic does not give a permanent preparation, nor does it obviate bunching of the cells which are constantly in motion. Small nongranular lymphocytes, closely resembling erythrocytes, can also be easily missed, as they do not take the stain readily.

DESCRIPTION OF CELL TYPES

In general, the white cells of the guinea-pig closely resemble those of man, except that they are larger. In addition, certain cells contain Kurloff bodies. In the description of the cell types, the order of ease of identification was followed.

Eosinophilic Leukocytes.—These cells are approximately twice the diameter of the red cells. The nucleus, which stains lavender, is usually bilobular and coarsely reticular; the granules are oval and stain terra-cotta. The cells are fragile.

Basophilic Leukocytes.—The basophils are larger than the eosinophils. The nucleus, which stains blue-lavender, is usually polylobular. The granules, staining deep purple, are clustered and are larger than the eosinophilic granules. These cells are fragile and are easily dissolved during the process of staining.

Neutrophilic Leukocytes.—The neutrophils are slightly smaller than the eosinophilic cells. The nucleus stains purple and is coarsely reticular and polymorphous. The granules are small and stain redder than those of the eosinophils. Threadlike streamers are frequently found connecting the granules.

Lymphocytes.—The lymphocytes present some difficulties, since their form and structure indicate three distinct types with intermediate variations.

One type resembles the small lymphocyte of man and is as large or slightly larger than an erythrocyte from the guinea-pig. The nucleus stains purple, is coarsely reticular, and contains from one to three

3. Dunn, J. S.: The Oxydase Reaction in Myeloid Tissues, J. Path. & Bact. **15**:20, 1911. Graham, G. S.: The Oxidizing Ferments of the Myelocyte Series of Cells and its Demonstration by an Alphanaphthol-Pyronin Method, J. M. Research **35**:231, 1916; Benzidine as a Peroxidase Reagent for Blood Smears and Tissues, ibid. **39**:15, 1918.

4. Von Domarus, A.: Methodik der Blutuntersuchung, Berlin, Julius Springer, 1921, p. 489.

nucleoli. The nucleus may be circular, oval or kidney-shaped. A pale blue cytoplasmic halo surrounds it. The cytoplasm itself is blue-gray. A few azurophilic granules are occasionally seen.

The second type of lymphocyte resembles the one just described, except that it contains neither paranuclear halo nor granules and that its cytoplasm stains an even, faint blue. Both small and large forms are found. The large form is not unlike a monocyte.

The third contains a lavender nucleus and a faintly even-staining blue cytoplasm. From 3 to 26 azurophil granules are contained within the cell. In shape, the cells are frequently round but often rectangular. These cells vary in size from that of a red corpuscle to that of a monocyte.

Monocytes.—The monocytes are approximately twice the size of the red cells. The nucleus may be oval, oblong or variously distorted. The nucleus of the monocyte is distinctive in character, since it is finely reticular and stains light purple. Its average size is about one-third to one-half the diameter of the cell. The cytoplasm is abundant, stains faintly blue and contains many dustlike granules.

Kurloff Body.—The cell containing the Kurloff inclusion body is not unlike the monocyte in its structural and staining details. Occasionally, such a cell may have a diameter four times that of a red cell. In preparations stained with Wright's stain, the Kurloff body may be either red, blue-red or purple. It varies in size from an azurophilic granule to a mass larger than the nucleus of the cell in which it is contained. It may even be as large as twice the diameter of a red cell.

In supravital preparations, the Kurloff body, because it is dead material, stains quickly as a homogeneous globoid mass, sharply differentiated from the living cell in which it is contained. It is seen frequently in the form of a spireme-like thread contained in a vacuole. Because this spireme-like mass is in constant motion, some investigators have considered it to be a living organism. Close observation, however, points to the fact that this vibratory motion is brownian movement which occurs after any living cell has been killed by absorption of dye.

THE FORMATION OF THE KURLOFF BODY

Theories of Formation of Kurloff Body.—Many theories have been advanced to explain the origin and nature of the Kurloff body. According to Weidenreich,[5] Kurloff considered these as vacuoles which are filled with a substance secreted by the cells. "Jolly and Acuna also observed acidophilic vacuoles which were found in 7 per cent of the large cell forms of the guinea-pig but which were lacking in embryonic

5. Weidenreich, F.: Leucocyten, Weisbaden, J. F. Bergmann, 1911.

forms."[5] Burnett[6] noted one or more vacuoles, or round bodies, which were almost as large as the nucleus. He was inclined to consider them degenerating mononuclears. Weidenreich[5] stated that Kurloff bodies were aggregations of coalesced masses. Ciaccio[7] believed them to be formed from nuclear extrusions. Ross,[8] Senez[9] and others considered them to be protozoan in nature. Schilling[10] apparently showed that Kurloff bodies were phagocytosed protoplasmic inclusions which were undergoing degeneration within the cell, their origin being in the blood elements. He also stated that they were resident in the bone marrow, spleen and places of destruction of the blood and that they are increased in infected animals. Pappenheim[11] altered his theories frequently. At one time he believed the Kurloff body to consist of azur granules; another time, he considered it a parasite capable of sporulation. Ross[8] considered it a parasitic lymphocytozoon which gave rise to free swimming spirochetes.

Bender[12] considered Ross' theory unsubstantiated and concluded that a relationship existed between Kurloff bodies and eosinophils. Bender and De Witt[13] asked an interesting question, "If the Kurloff body is a parasite, why should it be limited to the guinea-pig?" Lewis[14] noted engulfed living cells in hanging-drop cultures of whole blood of the frog. "The occurrence of ingested dead white cells within the large monocytes was common but the presence of living mononuclears within others of the same type was so rare that it attracted our attention. . . . The factors . . . are totally unknown but they undoubtedly are pathological . . ."

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6. Burnett, S. H.: Clinical Pathology of the Blood of Domesticated Animals, Ithaca, N. Y., Taylor and Carpenter, 1908.

7. Ciaccio, C.: Ricerche sui mononucleati a corpo incluso della Cavia, Anat. Anz. **30**:517, 1907.

8. Ross, E. H.: The Development of a Leucocytozoon of Guinea-Pigs, Proc. Roy. Soc., London **85**:67, 1912.

9. Senez, A.: The Kurloff Bodies, Rev. d. Inst. bacteriológico **3**:61, 1923; abstr., J. A. M. A. **80**:1107 (April 14) 1923.

10. Schilling, V.: Ueber Kierloffsche Korperchen beim Meerschweinchen, Folia haemat. **7**:225, 1909.

11. Pappenheim, A.: Ueber neuere Festellungen zur Natur der sogenannten Kurloffkörper in den grossen Lymphozyten des Meerschweinchenblutes, Folia haemat. **17**:183, 1913-1914. Pappenheim, A., and Ferrata, A.: Ueber die Verschiedenen lymphoiden Zellformen des normalen und pathologischen Blutes, u. s. v. (Am meerschweinchen demonstriert), Folia haemat. **10**:155, 1910.

12. Bender, L.: Kurloff Bodies in the Blood of Guinea-Pigs, J. M. Research **44**:383, 1924.

13. Bender, L., and DeWitt, L. M.: Haematological Studies on Experimental Tuberculosis of the Guinea-Pig, Am. Rev. Tuberc. **8**:138, 1923.

14. Lewis, W. H.: The Engulfment of Living Blood Cells by Others of the Same Type, Anat. Rec. **31**:43, 1925.

Observations on the Kurloff Body.—Stained, fixed and supravital preparations were used with success in observing the structure of the Kurloff body. It appeared as an evenly stained homogeneous mass in fixed smears and frequently as a homogeneous fluid in supravital preparations. The spireme-like formation was never seen in smears stained by the Wright method but was observed only in wet preparations. In the latter, mononuclear forms were often seen to be phagocytosing other elements of the blood. The phagocytosed cells were not limited to one type. Although the predominating type was the lymphocyte, monocytes, basophils and eosinophils were also observed undergoing destruction. Erythrocytes in the process of phagocytosis were not seen.

The following series of events leads to the conclusion, first suggested by Schilling,[10] that phagocytosis must be an important factor in the formation of Kurloff bodies:

1. *Phagocytosis.*—Phagocytosis of cells by others having the appearance of monocytes was best noted in supravital preparations. Frequently, various stages of phagocytosis of cells were also observed in fixed preparations. The intact cell showing the cell wall could be clearly made out.

2. *Cellular Death.*—This process was followed in supravitally stained preparations by noting the differences in staining characteristics of the nuclei of the phagocytosing and phagocytosed cells. The nucleus of the former remained unstained, while the latter became deeply stained.

3. *Obliteration of the Cell Wall.*—Occasionally, the wall of the phagocytosed cell was seen to be penetrated by the digestive fluids of the cell in which it was contained, thereby destroying the wall.

4. *Nuclear Disintegration.*—The nucleus of the phagocytosed cell was observed to change to a spongy mass and to take on a crenated appearance due to the digestive processes. Various stages of this process were seen in fixed smears. It has been referred to by other observers as the spore formation stage of the protozoan responsible for the formation of the Kurloff body.

5. *Condensation to Form the Kurloff Body.*—Many of the Kurloff bodies appeared as spireme-like threads contained within a vacuole when stained with 1 per cent alcoholic neutral red. This form was never seen in fixed smears, no matter how delicately stained. The full significance of the phenomenon is not yet clearly understood, since Kurloff bodies with homogeneous staining masses were also observed. It may be possible that two different processes contribute to the production of Kurloff bodies.

6. *Digestion.*—Since all sizes of Kurloff bodies were noted both in the fixed smears and in supravital preparations, it is assumed that a small Kurloff body indicates a phase in the process of digestion, in which the mass finally disappears.

THE DIFFERENTIAL COUNT OF THE NORMAL GUINEA-PIG

Counts of Previous Investigators.—The differential counts of previous investigators (table 1) show wide variations. These differences may be due to the lack of a uniform classification or to the fact that the published averages were based on too small a series of

animals. Klieneberger and Carl [15] determined their average count of eosinophils of 13 per cent on smears from six animals in which the range varied from 0.5 to 39 per cent. It was not always possible to find the data from which the percentage counts were calculated. It therefore became necessary to determine what could be considered a normal differential count by obtaining many smears over a long period of time from a large random sampling of apparently normal animals.

Differential Count of the Normal Guinea-Pig.—The distribution of cell types in a series of 303 counts of 100 cells each, forty-two guinea-pigs being used, was determined statistically by calculating the means,

TABLE 1.—*Differential Counts of Certain Investigators*

Observer	Lymphocytes, per Cent	Large Lymphocytes, per Cent	Small Lymphocytes, per Cent	Neutrophils, per Cent	Eosinophils, per Cent	Basophils, per Cent	Large Mononuclears, per Cent	Typical Monocytes, per Cent	Kurloff Bodies, per Cent	Transitionals, per Cent	Lymphocytes containing Kurloff Bodies, per Cent
Bender and DeWitt (Am. Rev. Tubere. **8**:138, 1923)	35-55	..	..	35-60	3-4	1	5-8	..	..	0-3	..
Betances (La Granulation Azurophile, 1918)	30-35	..	..	40-50	1	..	..	..	..	..	15-20
Burnett (Clinical Pathology of the Blood of Domesticated Animals, 1908)	47.3	..	..	31.5	10.7	0.37	10	..	..	..	..
Kanthack and Hardy (Clinical Pathology of the Blood of Domesticated Animals, 1908)	24	..	..	62	2-3	0.7	11	..	..	..	..
Klieneberger and Carl (Die Blut Morphologie der Laboratoriums-Tiere, 1912)	..	13.5	33	38.5	13	0.85	0.5	..	..	0.65	..
Kurloff (Clinical Pathology of the Blood of Domesticated Animals, 1908)	30-35	..	..	40-50	10	..	15-20	..	..	..	..
Lyons and Van de Carr (Unpublished experiments)	47	..	..	32.25	0.30	0.64	6.58	..	6.15	..	..
Schilling (Folia haemat. **7**: 225, 1909)	65-70	..	..	25-30	1-3	1-3	..	1-2	1-2	..	..

standard deviations and coefficients of variation, with their respective probable errors (table 2).

It becomes apparent that the predominating cell is the lymphocyte with a mean of approximately 75 per cent and a standard deviation of 9 per cent. This means that 68 per cent of the counts from a large random sampling of normal guinea-pigs would have lymphocytes varying between 66 and 84 per cent of the total cells counted. The constancy of the lymphocyte count is shown by the low coefficient of variation which is expressed as $\frac{100\ SD}{mean}$; the second, third and fourth types, in order of constancy, are the neutrophils, the monocytes and the cells containing the Kurloff bodies.

15. Klieneberger, C., and Carl, W.: Die Blut Morphologie der Laboratoriums-Tiere, Leipzig, A. Barth, 1912.

The coefficients of variation of the eosinophils and basophils are much higher than those of other cell types. This is due to the fact that many counts do not show eosinophils or basophils.

In order to test the validity of the normal count as determined by the statistical method, forty-five and sixty-seven counts were made from two slides from animals 50 and 61, respectively. The means, standard deviations and coefficients of variation of the counts from these guinea-pigs were compared with the measurements of the entire group (table 2).

TABLE 2.—*Comparison of Counts of Two Guinea-Pigs (50 and 61) with the Group Count* *

Cell Types		Group Representing 42 Guinea-Pigs (303 Counts)	Guinea-Pig 50 (45 Counts)	Guinea-Pig 61 (67 Counts)
Lymphocytes	M	74.69 ± 0.36	69.93 ± 0.96	76.09 ± 0.33
	SD	9.17 ± 0.25	9.60 ± 0.68	4.00 ± 0.23
	CV	12.28 ± 0.33	13.73 ± 0.99	5.26 ± 0.31
Neutrophils	M	15.42 ± 0.31	13.58 ± 0.33	13.10 ± 0.30
	SD	7.98 ± 0.22	3.26 ± 0.23	3.65 ± 0.21
	CV	51.75 ± 1.76	24.00 ± 1.80	27.86 ± 1.74
Monocytes	M	4.99 ± 0.12	3.02 ± 0.13	6.10 ± 0.21
	SD	3.02 ± 0.08	1.33 ± 0.09	2.56 ± 0.15
	CV	60.52 ± 2.18	44.04 ± 3.69	41.97 ± 2.84
Eosinophils	M	2.41 ± 0.11	10.22 ± 0.28	1.76 ± 0.12
	SD	2.93 ± 0.08	2.77 ± 0.20	1.50 ± 0.09
	CV	121.58 ± 6.62	27.10 ± 2.06	85.23 ± 7.75
Basophils	M	0.44 ± 0.02	0.24 ± 0.06	0.49 ± 0.03
	SD	0.54 ± 0.02	0.56 ± 0.04	0.70 ± 0.04
	CV	122.73 ± 6.74	233.33 ±54.73	142.86 ±18.69
Cells containing Kerloff bodies	M	2.06 ± 0.06	3.04 ± 0.20	2.45 ± 0.14
	SD	1.67 ± 0.04	2.04 ± 0.14	1.75 ± 0.10
	CV	79.61 ± 3.28	67.10 ± 6.58	71.43 ± 5.89

* In the table, M indicates the mean; SD, the standard deviation; CV, the coefficient of variation; the numbers following the ± signs are the probable errors of these measures.

It will be noted that in every case but one the mean value of a cell type falls within one standard deviation of the group count. The exception is that of the count of eosinophils of animal 50, in which the mean falls within three standard deviations from the mean of the group. This is entirely within the range of probability, since normal guinea-pigs may have a count of this magnitude (ten or greater) in 0.3 per cent of the cases, provided the group is a large one. Furthermore, this animal (50) may be considered normal since all the other percentages of the cell types fall close to the means of the count for the group.

The calculation of means, standard deviations and coefficients of variation for the counts of the cells on a single slide (guinea-pigs 50 and 61) proves that considerable variation may be encountered under

such conditions. In some cases it is even greater than the variation encountered among counts on a group of animals (table 2).

Coverslip versus Slide Preparations.—Advocates of the coverslip method of making blood films have agreed that these preparations are superior to those made on slides, because in the latter the heavier cells are drawn to the periphery of the slide and the distribution is altered. An experiment was done to test the validity of this contention. Three slides were made, and 100 cells per slide were counted: (1) along a line parallel with the length of the slide and at the periphery of the smear; (2) along a line at an angle of 45 degrees across the slide; (3) along a line step-wise across the slide. The results of these three counts are shown in table 3.

It was found that the counts in every case fell within one standard deviation of the group. If the probability of variation around the mean (standard deviation) is taken into consideration, no advantage can be ascribed to the coverslip over the slide method as far as distribution of cells is concerned.

TABLE 3.—*Results of Three Blood Counts*

	Lymphocytes	Neutrophils	Monocytes	Eosinophils	Basophils	Kurloff Bodies
(1).....	70	10	7	10	0	3
(2).....	76	13	4	4	0	3
(3).....	75	9	4	7	0	5

The question of variations in cell count due to experimental infection of the guinea-pig remains open for future investigation.

THE RELATION OF THE KURLOFF BODY TO OTHER CELL TYPES

Kurloff Bodies and Eosinophils.—Is there any correlation between the number of cells containing Kurloff bodies and the number of eosinophils? This is a question of primary importance since Bender [12] believed that such a relationship does exist. The statistical correlation (Pearson coefficient) between these two cells was found to be -0.0229 ± 0.0386. Since the probable error (0.0386) is greater than the correlation itself (-0.0229), a reliable relationship between the two is not evident, and the correlation itself is too low to be significant.

Kurloff Bodies and Monocytes.—Does an association exist between the number of cells containing Kurloff bodies and the number of monocytes? Is this association negative, so that it could be said that the greater the number of cells containing Kurloff bodies, the fewer monocytes present in each 100 cells?

A correlation coefficient was calculated between these cell types, the result being 0.0646 ± 0.0386. This coefficient is again unreliable in terms of the probable error and is numerically insignificant.

Kurloff Bodies and Lymphocytes.—The correlation coefficient between cells containing Kurloff bodies and lymphocytes was calculated to be -0.2453 ± 0.0364. This correlation is low, but it is significant since it is greater than three times its probable error. It is a negative correlation; that is, as cells containing Kurloff bodies increase, lymphocytes decrease. What does this mean? Are these cells lymphocytes? This does not seem possible, since they are unlike lymphocytes but resemble monocytes morphologically. On the other hand, the second type of lymphocyte previously described in this paper may have some resemblance to, or possible relationship with, the monocyte. The cell containing the Kurloff body does not have a significant correlation with the latter, while the negative correlation with the lymphocyte may be due to the fact that the Kurloff body is found in cells of the second type. If this were true, it would appear that the Kurloff containing cell is a phagocytosing lymphocyte.

It may be that the Kurloff inclusion is formed by the destruction of lymphocytes which have been phagocytosed by some other cell, since it was observed that many phagocytosing cells contained lymphocytes undergoing destruction.

The correlation may also be a function of numbers, since the lymphocyte is the predominating cell of least variation, and any increase in another cell type might tend to make a more significant difference in the total number of the most common cell.

These are merely suggested explanations. The answer can be determined only by a finer classification of lymphocytes into definite subgroups, and subsequent correlation between these groups and the incidence of Kurloff bodies.

SUMMARY AND CONCLUSIONS

A. *Differential Blood Count of the Normal Guinea-Pig.*—1. There are three distinct morphologic types of lymphocytes in the circulating blood of the guinea-pig.

2. Evidence is presented that the fixed smear stained with a Romanowsky stain is preferable to supravital preparations for the counting of the blood cells, although the latter technic is useful in studying the behavior of cells and the formation of the Kurloff body.

3. Slide preparations of blood do not produce differential distribution of large cells toward the periphery of the smear.

4. The differential count of the normal guinea-pig varies between certain limits which have been statistically established.

5. Considerable variation in distribution of cell types may be encountered in a single smear.

B. *The Kurloff Body.*—1. That phagocytosis is a factor in the formation of Kurloff bodies is suggested by the observations of intermediate stages between beginning phagocytosis and complete disappearance of the phagocytosed cells, as indicated by variations in their size.

2. The Kurloff body appears to be dead material, since it stains readily with supravital dyes in contrast with the living cell in which it is contained.

3. Neither eosinophilic leukocytes nor monocytes correlate significantly with Kurloff bodies.

4. A low negative but significant correlation exists between lymphocytes and Kurloff bodies. When the Kurloff count is high, the lymphocyte count is low. This may mean that since the lymphocyte is the predominating cell type any variation in the other cell types will cause a greater and more significant variation in this group. It may mean that ingested lymphocytes become Kurloff bodies or that lymphocytes of the second type are phagocytosing cells containing Kurloff bodies.

PRIMARY ROUND CELL SARCOMA OF PERICARDIUM

REPORT OF A CASE *

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In 1918, the late Dr. I. Perlstein [1] of Chicago reviewed the literature on cardiac tumors. He found that the first primary sarcoma of the heart was described by Bodenheimer in 1865, and that thirty such cases had been reported since. In 1911, Erhenberg collected nineteen cases of cardiac sarcoma, and in 2,942 autopsies at Johns Hopkins Hospital, ten cardiac tumors were found, including one sarcoma. The most common primary cardiac tumors, in their order of frequency, are fibroma, myoma, fibromyoma and sarcoma. In Perlstein's compilation, eighteen cases occurred in males and ten in females; eight of these cases were limited to, or primary in, the pericardium. The type of cell varied; there were ten spindle cell and six round cell sarcomas. Pleural effusion was present in thirteen cases and pericardial effusion, in ten; the pericardial sac was partially or entirely obliterated in five.

J. C. Williams [2] reported a primary sarcoma of the parietal pericardium which was similar to that in the case which I report. In his case, there was a lobulated tumor of the parietal pericardium adherent to the anterior thoracic wall, but the epicardium or myocardium was not involved. The growth invaded the diaphragm even to its peritoneal surface. Glandular involvement was not found. The microscopic picture was that of rather rapidly growing cells, a homogeneous, pink-staining intercellular substance, and many newly formed blood vessels. The chief difference in William's case and the one reported here lies in the fact that the former did not show any involvement of the epicardium or myocardium.

REPORT OF A CASE

Clinical History.—A negro, aged 35, was admitted to the John Sealy Hospital on Dec. 22, 1921. He was able to walk to the hospital. His chief complaint was of pain in the region of the stomach and of dyspnea. The temperature was 100.4 F.; the pulse rate 72; respiration, 28, and blood pressure 98 systolic and 80 diastolic. There was a history of pneumonia one year previously and of influenza three years previously; also of gonorrhea and syphilis.

The present illness appeared to have begun four weeks before with pains in his chest and abdomen. He vomited several times and the stomach remained

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* From the Department of Pathology, University of Texas.

1. Perlstein, I.: Sarcoma of the Heart, Am. J. M. Sc. **156**:214, 1918.

2. Williams, J. C.: Primary Diffuse Small Cell Sarcoma of the Parietal Pericardium, New York M. J. **71**:537, 1922.

upset afterward. He had marked dyspnea and a more or less continuous cough. Pains began in the right infraclavicular region and radiated to the abdomen, then up to the left side of the chest to the infraclavicular region of that side.

Physical Examination.—The patient was well nourished and apparently in good condition. The breath was foul and the tongue heavily coated; the abdomen was distended with gas; the liver and spleen were normal in size. There was an area of dulness in the epigastrium about 3 inches (7.6 cm.) in circumference in the midline and apparently over the stomach. There was some tenderness in this area but no palpable masses. There was a great increase in the cardiac dulness on the left side; over the precardium a heaving impulse was present; the point of maximum impulse was visible in the sixth and seventh interspaces 15 cm. from the midsternal line; right cardiac dulness extended 5 cm. from the midsternal line in the third interspace. The aortic dulness extended from 6 cm. to the left to 5 cm. to the right of the midsternal line. There was a loud systolic murmur, blowing in character, over the base of the heart. The pulse rate was 100. The roentgenogram was thought to show a probable aneurysm and pericardial effusion. Fluroscopic examination revealed a greatly enlarged cardiac shadow, but there was no encroachment on the structures in the posterior mediastinum. There was some decrease in tactile fremitus over the base of the right lung, and dulness over the bases of both lungs, posteriorly.

The blood Wassermann test was positive (4 plus); the urine showed a trace of albumin; the blood count was practically normal.

Treatment and Course.—On Jan. 7, 1922, about 150 cc. of a blood tinged fluid was removed from the right pleural cavity. The temperature varied from 94 to 97 F. most of the time; the pulse rate from 60 to 100, becoming weaker and not palpable at the wrist; the respiration ranged between 20 and 28. A marked edema of the feet and legs developed. Death occurred on Jan. 13, 1922.

Autopsy.—Autopsy performed six hours after death revealed the body of a young negro, showing marked emaciation, and a great deal of edema of the feet and legs. There was no lividity, and rigor was not marked.

The thoracic cavity was opened in the usual manner, but the lungs were not visible. A diffuse tumor mass occupied the midline of the mediastinum and spread out over the outer surface of the pericardium in such a manner that the only point of entrance into the pericardial sac was high up over the base of the heart opposite the second rib. Here a small area was noted in which the tumor was thinner, and the usual pericardial sheen could be made out to some extent. The cavity was opened by cutting from base to apex through a mass covering the parietal pericardium which was from 1 to 2 cm. in thickness. The visceral and parietal pericardium were connected over all parts by scattered fibrinous bands which were broken through without a great deal of difficulty. The pericardial layers were covered with grayish yellow rounded nodules, varying in size, with a broad base, and projected out from a thinner investing layer of the tumor tissue. This structure completely surrounded the heart, and invaded the muscle of the heart from one-half to three-fourths the thickness of the wall of the heart. There was almost no fluid in the pericardial sac. The mitral valve was normal. The aortic valve, which was viewed from above, was also normal. The aorta showed linear and longitudinal striations, but these were not marked. The heart itself was enlarged to three or four times its normal size. The parietal pericardium was found to be invaded by tumor tissue in all parts. Along the entrance of the inferior and superior venae cavae into the pericardial sac, an extension of the neoplasm passed from

the pericardium to epicardium. At the base of the pericardium, an apron of tumor tissue extended down to the diaphragm and infiltrated this structure to the peritoneal surface. The tumor mass was everywhere of a grayish-yellow, nodular appearance. On section, these nodules were seen to be soft and homogenous with no evidence of trabecular, Only one mediastinal lymph node was found enlarged, but it was discrete and easily separated. It consisted of typical tumor tissue with hemorrhagic infiltrations. No other nodes were found enlarged.

The left lung was free from adhesions; it crepitated throughout, except for two small areas in the base of the lower lobe. These areas presented an appearance similar to that of the tumor mass. There was no fluid in the left pleural cavity. Peribronchial lymph nodes were not enlarged.

On the right side, the tumor spread directly on to the medial and anterior aspect of the surface of the lung. The entire mesial surface of the lung was adherent to the tumor mass, which extended over on the anterior surface for about 2 cm. The pleura on the posterior surface was about 5 mm. thick, of a cartilaginous feel and grayish. There were a few fibrous adhesions in the apical region. A few nodules similar to those seen in the left lung were seen at the base of the right lung. There were about 100 cc. of a reddish brown fluid in the right pleural cavity.

The tumor mass in the mediastinum occupied the anterior portion, and the deeper structures were not involved. The bulk of the tumor was in the inferior portion, forming a fringe around the right inferior aspect of the heart and invading the diaphragm.

Marked gross changes were not found in any of the organs. Other secondary lesions or possible primary growth was not found.

Microscopic Examination.—The neoplasm was composed of a diffuse mass of cells, a rather abundant amount of intercellular substance and many newly formed, thin-walled blood vessels. The cells were variable in size as well as in structure. Some were small, round and mononuclear, with a scant cytoplasm and with more or less uniform, deeply staining nuclei; while others were rather large and round, and contained a large amount of eosinophilic cytoplasm; the nuclei were eccentrically placed and were not so uniform or deeply stained as those in the smaller cells. Between these two extremes, one saw all the gradations of rapidly developing cells. Some cells were large, with pink homogenous cytoplasm and multinucleated, but these were seen only occasionally. The intercellular material was rather abundant, and, in some fields was accumulated in bundles as a homogenous pink-staining substance. There was some newly formed fibrous tissue scattered through the sections. There were many newly formed blood vessels, and practically all showed an endothelial lining. There was no hemorrhage in any of the sections, except that taken from the lymph node, where the blood vessels were not so well formed.

COMMENT

In reviewing the case one is confronted with two problems of interest: Where did this tumor arise? What is the nature of the growth?

It seems that the primary growth must have been in the pericardium or epicardium, in view of the following facts: (1) the preponderance of the tumor tissue in these two structures; (2) the finding of only

one lymph node which contained tumor tissue; (3) the absence of tumor growth, except that in the mediastinum, and (4) the freedom of the other structures in the mediastinum. This introduces another question: Is it primary in the epicardium or pericardium? Clinically, it seems rather improbable that a patient with primary involvement of the epicardium or myocardium could live long enough to get such an extensive involvement of the pericardium. There was a great deal more tumor tissue in the right portion of the pericardium than in the left, and if the growth was primary in the epicardium or myocardium, why should there not have been more or less equal distribution throughout the pericardium?

As to the nature of the neoplasm, there seem to be three growths which may be confusing on superficial examination, namely, endothelioma, lymphoblastoma and small round cell sarcoma.

The following facts, seemingly, are evidence that a diagnosis of lymphoblastoma could not be made: (1) the presence of tumor tissue in only one lymph node, while all others were free from the growth; (2) the great variation in the size of the tumor cells; (3) the rather abundant amount of intercellular material; (4) the absence of infiltration of the capsule of the enlarged node by tumor tissue; and (5) the fact there was no matting together of the structures of the mediastinum as in lymphoblastoma.

Endothelioma can be eliminated. According to Ewing,[3] the form of cell in endothelioma is polyhedral, often pavement in type, and occasionally cylindric in shape. Again he stated, "The cells have a well defined cell membrane, relatively clear cytoplasm, and small, pale, vesicular nucleus with minute multiple nucleoli." In endothelioma, one expects the cells to have a more or less definite arrangement in rosettes or columns, alveolar, plexiform, perivascular, or occasionally diffuse. One would also expect, if this was an endothelioma, to have some proliferation of the endothelial elements of the blood vessels. This is not the case. Ewing stated that he has been unable to detect definite formation of intercellular fibrils in endothelioma. Since none of these characteristics are evident in the sections of the neoplasm now reported, it seems justifiable to eliminate endothelioma.

The relation between the large cells and the intercellular substance demonstrates the fact that the growth arose from connective tissue structures. Consequently, I am of the opinion that the neoplasm did not arise from the serous coat of the pericardium, but rather from the subpericardial fibrous tissue. Taking all the facts into consideration, a diagnosis of primary small round cell sarcoma of the pericardium appears warranted.

3. Ewing, James: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1919, p. 290.

Laboratory Methods and Technical Notes

A NEW INDIRECT METHOD FOR TAKING BLOOD PRESSURE IN ANIMALS *

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Experimental studies on chronic hypertension in this laboratory have made it necessary to take repeated readings of blood pressure on animals. In an effort to find a suitable method, a review of the literature was made, and all of the older procedures were tried. None proved entirely satisfactory. A new method was devised which overcomes many of the difficulties. My objects in this paper are: (1) to review the literature of the development of the various methods of estimating blood pressure, and (2) to describe the new method devised in this laboratory.

REVIEW OF THE LITERATURE

CANNULA METHOD

1. *History of Development.*—In 1733, more than 100 years after Harvey's [1] memorable work, an English scientist, Stephen Hales,[2] demonstrated and measured blood pressure. By means of brass piping, he connected a glass tube 9 feet high and ⅙ inch in diameter with the left crural artery of a horse. The blood rose in the tube 8 feet and 3 inches above the level of the left ventricle. It continued to rise and fall from 2 to 4 inches with each heart beat. The disadvantages of this method were, of course, the awkwardness of the long tube and the rapid coagulation of the blood. In 1828, Poiseuille [3] solved both these difficulties. He introduced the U shaped mercury manometer which reduced the space required for measurement to less than one-thirteenth. He was able to retard coagulation by filling the tube leading from the artery with a saturated solution of sodium carbonate.

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* Read before the Minnesota Pathological Society, February, 1927. An abstract of this paper appeared in Society Transactions, Arch. Path. 3:911 (May) 1927.

* From the Department of Pathology, University of Minnesota.

1. Harvey, William: The Works of William Harvey, by Robert Willis, Printed for the Sydenham Society, London, Adlard & Son, 1847.

2. Hales, Stephen: Statical Essays Containing Haemostatics, London, 1733, vol. 2, quoted by Starling: Human Physiology, Philadelphia, Lea & Febiger, 1926, p. 804.

3. Poiseuille, quoted by Tigerstedt: Physiologie des Kreislaufes, vol. 1, p. 104 and vol. 3, p. 143.

This made prolonged experiments possible. In 1847, Ludwig [4] adopted the mercury manometer so that graphic records could be made.

2. *Development of Improvements in Apparatus.*—The numerous experiments requiring the use of the direct method have led to improvements in the apparatus. One of the first important steps was taken by von Kries,[5] who used a narrower tube for the one leading from the artery, since he found that it gave results more nearly equal to the actual mean pressure. Marey [6] applied the same principle in using a narrower tube for the one containing the mercury. This instrument, which Marey called a compensated manometer, gives accurate readings of mean pressure. Three different types of cannulas have been used.

(*a*) A T cannula in the artery, which does not obstruct the flow and measures the lateral pressure, i.e., the force exerted by the blood against the arterial wall.

(*b*) A straight cannula, which, when inserted in the artery measures the end pressure. This is equal to the lateral pressure plus the pressure due to the velocity of the blood stream. Thus, a straight cannula in the carotid, which leaves the aorta practically at right angles, measures the lateral pressure in the aorta. The difference between end pressure and lateral pressure, according to von Recklinghausen [7] and Staehelin and Müller,[8] is only a few millimeters of mercury.

(*c*) The inertia of mercury is so great that it does not record the sudden variations in blood pressure produced by each heart beat. Therefore, neither the straight nor the T cannula is able to record more than the mean pressure. This value corresponds with the arithmetic mean of the maximum (systolic) and minimum (diastolic) pressures. In order to have more detailed records of pressure changes inside the vessels, a cannula with maximum and minimum valves was constructed. It records only maximum and minimum pressures.

3. *Results Obtained by Various Investigators.*—These three types of cannulas have been used in the study of blood pressure in the various arteries of laboratory and other animals. Most of the published results are records of mean pressure. The arteries commonly used have been the carotid, femoral, brachial and the aorta. They differ in size and in

4. Ludwig, C.: Beiträge zur Kenntniss des Einflusses der Respirationsbewegungen auf den Blutlauf in Aortensysteme, Arch. f. Anat., Physiol. u. wissensch. Med., 1847, p. 242.

5. Von Kries: Ueber die Bestimmung des Mitteldruckes durch das Quecksilbermanometer, Arch. f. Anat. u. Physiol., 1878, pp. 419-440.

6. Marey, I.: Annales des sciences naturelles; 4 serie zoologie **8**:350, 1858.

7. Von Recklinghausen, Heinrich: Ueber Blutdruckmessung beim Menschen, Arch. f. exper. Path. u. Pharmakol. **46**:78, 1901.

8. Staehelin, R., and Müller, Aloys: Kritik der gewöhnlichen Blutdruck Messungsmethoden, Ztschr. f. d. ges. exper. Med. **46**:263, 1925.

distance from the heart. Therefore, it might be expected that the readings in each vessel would differ considerably. This branch of the dynamics of the circulation has been worked out by Poiseuille and by Dawson.

Poiseuille,[8] working on dogs, obtained identical mean pressures when he had the manometer connected at the same time with the carotid and brachial arteries, the carotid and abdominal aorta, the carotid and renal, or the axillary and crural, arteries. In horses, he did not find any difference in pressure when the manometer was united to the carotid and a small muscular artery of the thigh. This led him to believe that the mean pressure of different arteries was equal and independent of their distance from the heart. Dawson [9] has since shown that the mean pressure is practically constant throughout the large systemic arteries, until such small ones as those in the circle of Willis are reached. The diastolic pressure is also practically constant in the larger arteries. He found that the diastolic pressure in the femoral artery is slightly lower than in the carotid (femoral pressure, 95; carotid pressure, 103, in accordance with Hürthle [10]). Janeway [11] stated that "in the larger systemic arteries used for the clinical estimation of blood pressure, the lateral pressure, especially the diastolic, closely approximates that within the aorta."

There is, however, a wide range of variation of blood pressure in any individual. For that reason the values, even in individuals of the same species, vary almost as widely as values in different species. An example of this variation is seen in Crile's [12] records of mean carotid pressure in 100 dogs. His readings average 125, the highest being 170 and the lowest, 80. Investigators who have had experience with determinations of blood pressure in animals have been unable to find any correlation between size or weight and blood pressure.

4. *Summary.*—The direct method of estimations of blood pressure has been and is of great value in relatively short experimental investigations. The straight and the T cannulas give the mean pressure in the vessel used. The maximum and minimum valve cannula gives a more accurate record of the changes going on in the vessel. This method is most valuable for comparison with the clinical indirect method which also measures maximum and minimum pressures.

The direct method, however, has many disadvantages. (*a*) Anesthesia and operative procedures are necessary, both of which are bound

9. Dawson, Percy M.: The Lateral Blood Pressures at Different Points of the Arterial Tree, Am. J. Physiol. **15**:244, 1905-1906.

10. Hürthle, Karl: Beiträge zur Haemodynamik, Arch. f. d. ges. Physiol. **47**:1, 1890.

11. Janeway, Theodore C.: The Clinical Study of Blood-Pressure, 1904, p. 31.

12. Crile, George W.: Blood-Pressure in Surgery, 1903, p. 359.

to cause some variation from the normal blood pressure in the animal. (*b*) The method is inapplicable to man and in many cases to animals. (*c*) The blood pressure can be observed for only a few hours. The cannula method, then, is useless in experiments extending over days, weeks or months. (*d*) The artery has to be ligated following the taking of the tracing. It is no longer useful, and few other arteries in the same animal are available for further experiments. (*e*) The cannula method has definite limitations, whether a straight or a T cannula is used. Mercury is so heavy that it cannot follow rapid cardiac and respiratory variations in pressure.

For these reasons, it is desirable to have a simple, accurate method of taking repeated measurements of blood pressure in laboratory animals without anesthesia and without any operative intervention. A good many investigators have worked on the problem, and various methods have been published.

THE INDIRECT METHOD

1. *History of Development.*—The First Indirect Method: The first method of estimating blood pressure was simple. It consisted of palpation of a peripheral artery such as the radial. Two standards for measuring the tension were used; the digital pressure required to obliterate the artery until a second more distal finger could no longer feel the pulse and observation of the change in the pulse wave during gradually increased pressure on the artery. By either of these methods marked changes in pressure will be detected, but the methods are not accurate. The chief reason for the inaccuracy is the variation in size of radial arteries. The larger the artery, the higher the pressure seems to feel on palpation. This is due to the fact that a solid object such as the finger measures total and not unit pressure.

The First Sphygmograph: The first sphygmograph to measure blood pressure was constructed by Vierordt[13] in 1855. Pressure was applied through a solid block and therefore, like the finger, it measured total rather than unit pressure. The results varied, depending on the person using the instrument. The apparatus was altered slightly by subsequent investigators, but they continued to use the same principle of solid pressure on the artery.

Systolic Pressure: The substitution of fluid compression was made by von Basch of Vienna in 1876. His sphygmomanometer consisted essentially of a bag containing fluid as the compressing medium connecting with a mercury manometer. He was the first to measure pressure per unit surface. The next advance was that of Potain, in 1899,

13. Vierordt, quoted by Janeway: The Clinical Study of Blood-Pressure, 1904, p. 45.

who substituted air for fluid medium. The sphygmomanometers of both von Basch and Potain measure the pressure necessary to obliterate the artery when it is compressed against a bony surface. This is practically equal to the systolic end-pressure. However, the position of the artery on the bone influences the readings so much that even von Basch and Potain obtained variable results. Tigerstedt considered von Basch's measurement from 32 to 78 mm. too high. The sphygmomanometer of von Basch with the modification of Potain represents the first indirect method of determining systolic pressure; that is, the pressure necessary to obliterate the pulse.

Diastolic Pressure: At about the same time the first instrument to register diastolic pressure was constructed by Marey. His idea was to compress the vessel from all sides. He used a tight metal box filled with water into which the hand and forearm were inserted through a rubber collar. The box was connected with a mercury manometer and a reservoir so that the pressure could be raised. The hand could be watched through a glass window. The pulse waves were transmitted by the water to a tambour. As the pressure was lowered, the pulsations suddenly increased in amplitude, became greater and then gradually declined. At the phase when the external pressure was sufficient to collapse the vessels, the skin of the hand became white and later the color gradually returned. Marey believed that when the pulsations became greatest, the external pressure must be about equal to the pressure within the vessels. This stage of maximum pulsation has been shown to correspond accurately with the diastolic pressure.

Marey attempted to use a smaller apparatus on one finger to record the pulsations, but changes in volume were too slight. In 1895, Mosso constructed a more elaborate sphygmomanometer on the same principle. The two middle fingers of each hand are enclosed in the apparatus, and pressure changes in them are recorded. Fairly accurate results were obtained, and the instrument has been much used in physiologic laboratories.

Circular Compression by Air: Marey's observations, however, had suggested a new criterion for systolic pressure, namely, the change in color of the skin. This principle was used by von Kries,[5] in 1875, to measure capillary pressure and also by Gärtner [14] in the construction of his tonometer. This tonometer, which was introduced in 1899, consisted of a pneumatic ring, the inside of which was covered by a narrow rubber bag which could be filled with air. The bag, which fitted over the terminal phalanx of a finger, was connected with a rubber bulb and a mercury manometer.

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14. Gärtner, Gustav: Ueber einen neuen Blutdruckmesses (Tonometer), Wien. med. Wchnschr. **30**:1411, 1899.

In 1896, Riva-Rocci [15] and Leonard Hill,[16] working independently, perfected the first accurate sphygmomanometers that could be used in practice. The new principle was the use of a rubber bag, which could be inflated with air, to encircle the arm and compress the vessel. The Riva-Rocci cuff went completely around the arm and fastened with a special clamp. The Hill cuff went half way around the arm over the vessel and was held there by a leather cuff and buckle.

2. *Experimental Verification of Method of Circular Compression.*—A great deal of experimental work has been done with the Riva-Rocci and Hill cuffs chiefly because the various investigators have obtained such different results. On that account, the possible sources of error have been carefully studied. The most detailed and elaborate work has been done by von Recklinghausen [7] and by Erlanger.[17]

Application and Adjustment of Cuff: The most important result of their work has been a standard method of application and the adoption of a standard width for the cuff. The cuff must be adjusted so that it fits snugly but still does not exert pressure on the vessel. Janeway obtained readings as much as 30 mm. too high with a cuff that was applied loosely. The same restriction applies to the use of the Gärtner tonometer. Martin's investigations showed it to be inaccurate except when it fitted the phalanx exactly.

The site of application must also be taken into consideration. No matter what method is used, the compression of the vessel must be on a level with the heart. If the point of compression is below the level, the weight of the column of blood between the two levels will be added to the blood pressure, and it will be subtracted from it if the point of compression is above the level of the heart. Muscular relaxation must be complete, or the readings will be too high. Accurate results are impossible when the surrounding muscles are in a state of contraction. The maximal error due to loss in transmission of pressure through the tissues has been estimated by Janeway as 10 mm.

Width of Cuff: Von Recklinghausen [7] studied the results obtained with narrow and with wide cuffs and stated that any cuff less than 15 cm. in width gave readings which were too high, but that the error was practically negligible with the 15 cm. cuff. He believed that part of the pressure was lost in deforming the tissues. A narrow cuff tends to become cylindrical on inflation, and as much pressure is used to indent

15. Riva-Rocci: Un nuovo sfigmomanometro, Gazz. med. di Torino **50**:51, 1896.

16. Hill, Leonard, and Barnard, Harold: A Simple Pocket Sphygmomonometer for Estimating Arterial Pressure in Man, J. Physiol., 1898-1899, vol. 23 (Proc. Phys. Soc., p. 4).

17. Erlanger, Joseph: A New Instrument for Determining the Minimum and Maximum Blood Pressures in Man, Reports Johns Hopkins Hosp. **12**:53, 1904.

the tissues as to compress the artery. A wide cuff exerts its full pressure on the artery beneath on inflation, only a small portion being used to deform the tissues. A cuff from 12 to 15 cm. wide gives readings almost identical with intravascular pressure. An additional factor is the circumference around which a cuff is wound. A small limb, such as is found in children and laboratory animals, has less tissue to resist compression; so a narrower cuff can be used.

Erlanger's experiments showed that the length of artery compressed did not have any effect on the values for blood pressure. Readings were taken simultaneously, with arteriographs of different length, on the two femoral arteries. Each artery was dissected free from the surrounding tissue, and different lengths of the vessel wall were compressed. The readings were identical. The experiment showed that the artery itself offers practically no elastic resistance to compression. With the elimination of that factor, there was nothing left to cause the error with the narrow cuff except the resistance of the soft tissues surrounding the artery. Janeway experimented with different widths of cuffs on the thighs of dogs and found that a cuff 9 cm. wide was necessary. A cuff 3½ cm. wide gave results as much as 50 mm. too high. Both systolic and diastolic values were higher, so that with a cuff more than 4 cm. wide, the pulse pressure was practically unaffected. The same difficulty was encountered in the use of Gärtner's tonometer. Von Recklinghausen concluded from his experiments that the bag should cover the whole proximal phalanx instead of the 1.5 cm. width of the original apparatus.

As a result of these investigations, the use of the original Riva-Rocci 5 cm. cuff has gradually ceased. Martin,[18] Erlanger and Janeway each substituted cuffs 12 cm. wide in their respective sphygmomanometers. With proper application of a sufficiently wide cuff, accurate readings of the blood pressure may be obtained.

The Pressure the Sphygmomanometer Measures: Erlanger also investigated what pressure the sphygmomanometer measures. He concluded that it determines the systolic or maximum end-pressure of the artery occluded. He applied a sphygmomanometer connected with a maximum and minimum valve on the femoral artery of an animal and an arteriograph to the other femoral artery and took readings simultaneously. The compression of the artery by the arteriograph caused a rise in the maximum pressure, while the minimum pressure was scarcely affected. The diastolic or minimum pressure by the two methods practically corresponded. The rise in the maximum pressure was due to the addition of the velocity head to the pressure head. The

18. Martin, Alfred: Technisches über das Riva-Roccische Sphygmomanometer und Gärtner's Tonometer, München. med. Wchnschr. **50**:1021, 1903.

average error for the maximum pressure varied between 1 and 5 mm. With any width of cuff or any length of artery compressed, the determinations of extravascular blood pressure were always slightly in excess of the determinations of intravascular pressure.

3. *Criteria for Systolic Pressure.*—With the indirect method, there are several criteria for reading the systolic pressure.

Palpatory: The criterion here is the return of the pulse wave under compression. The pressure in the cuff of the sphygmomanometer is raised until the pulse cannot come through the wrist. The pressure is slowly lowered, and the level of mercury at which the first pulse is palpable in the radial artery is taken as the systolic pressure.

Auscultatory: In 1905, Korotkow [19] discovered that when the bell of a stethoscope is placed over the radial artery just below the cuff and the pressure is slowly released, a series of characteristic sounds are heard. These sounds have a definite relation to the systolic and diastolic pressure in the artery. Ettinger and Goodman and Howell [20] have distinguished five phases; (1) a sharp, clear sound which indicates the first passage of the arterial stream beneath the cuff; (2) the same tone dulled; (3) the same tone sharper and clearer; (4) the sudden dulling of that sound and (5), the disappearance of all sound. Warfield [21] showed that the appearance of the first sound corresponds with the systolic and the fourth with the diastolic pressure. Erlanger [22] showed that the cause of the sound depends on the production of a water hammer in the blood vessels below the compression cuff. The changes in pressure, produced by stopping the flow, throw the wall into vibration and produce a sound. When the pressure in the cuff is between systolic and diastolic pressure, some blood passes through the artery under the cuff with each pulse beat. This rapidly moving column of blood strikes the stationary column below the cuff, distends the arterial wall and causes it to vibrate. The auscultatory method is the one most commonly used. The readings are from 10 to 15 mm. higher than with the palpatory method.

Graphic: When a spring manometer is used and the pulsations are recorded with a writing point, the systolic pressure conforms with

19. Korotkow, quoted by Lang, Georg, and Manswetowa, Sophie: Zur Methodik der Blutdruckmessung nach von Recklinghausen und Korotkoff, Deutsches Arch. f. klin. Med. **94**:441, 1908.

20. Goodman, Edward H., and Howell, A. Alexander: Further Clinical Studies in the Auscultatory Method of Determining Blood Pressure, Am. J. M. Sc. **142**: 334, 1911.

21. Warfield, Louis M.: The Auscultatory Blood Pressure Phenomenon, Interstate M. J. **19**:856, 1912.

22. Erlanger, Joseph: Studies in Blood Pressure Estimation by Indirect Methods, Am. J. Physiol. **39**:82, 1915-1916.

the sudden abrupt increase in amplitude of the pulsations. The graphic method is used chiefly in physiologic laboratories.

Visual: The criterion here is the return of color to the skin of the blanched area. Gärtner developed this method on the basis of Marey's original observation. The finger is rendered anemic. The pressure in the ring is raised above systolic and then slowly released. The level of the mercury at which the color suddenly returns to the pale finger is taken as the systolic pressure.

4. *The Criteria for the Reading of Diastolic Pressure.*—(*a*) Palpatory. The level of mercury following the release of pressure at which the pulse becomes full and bounding is considered to equal the diastolic pressure.

(*b*) Auscultatory: The criterion most in use is the sudden dulling of the sound at the fourth phase.

(*c*) Graphic: When the external pressure is below systolic, the mercury in the U tube begins to oscillate. As the mercury falls, the oscillations increase in amplitude and are synchronous with the pulse. Finally, they decrease and disappear. The level of mercury at which the maximum excursion takes place is regarded as the diastolic pressure. This is called the principle of Marey. It was later experimentally proved by Mosso and by Howell and Brush.[23]

5. *Comparison of Direct and Indirect Methods.*—Before the advantages or disadvantages of the indirect method are pointed out, a brief summary of the experiments undertaken to confirm its accuracy will be given. Direct and indirect determinations of blood pressure have been made simultaneously in animals and in man. For obvious reasons, the technic of the cannula method has been perfected on animals, while that of the indirect method has been worked out on man. This explains the difficulty of accurate comparison.

In Animals: Mummery[24] put a Riva-Rocci cuff on one femoral artery and a cannula connected with a mercury manometer in the other. His experiments showed a small degree of error for the indirect method. Van Leersum[25] took direct readings of blood pressure on the femoral artery in rabbits and indirect readings on the carotid artery. He found that the two curves run parallel, although there was an average difference of 10.4 per cent. The indirect method gave the higher results. Tigerstedt stated that experiments in animals, in which determinations

23. Howell, W. H., and Brush, C. E., Jr.: A Critical Note upon Clinical Methods of Measuring Blood Pressure, Boston M. & S. J. **145**:146, 1901.

24. Mummery, P. Lockhart: A Comparison of Blood Pressure Readings Obtained Simultaneously with a Manometer and with a Sphygmomanometer, Proc. Physiol. Soc., J. Physiol. **32**:23, 1905.

25. Van Leersum, E. C.: Eine Methode zur Erleichterung der Blutdruckmessung bei Tieren, 1911, pp. 142 and 377.

of blood pressure were made on one femoral artery by means of a cannula and on the other femoral artery by a Riva-Rocci cuff, have shown almost complete agreement. He does not, however, give the details of the experiments. Both Mummery and van Leersum used only an ordinary mercury manometer, with which it is impossible to measure maximum and minimum pressures. The direct readings were therefore those of mean pressures. This fact alone would account for the higher results with the indirect method.

Simultaneous estimations in which the tonometric and the cannula methods were used were made by Backmann.[26] The pressures obtained with a cuff of standard width, 25 by 18 cm., were about the same as those with the direct method.

More accurate investigations were conducted by Erlanger. He studied intravascular and extravascular blood pressures in the femoral arteries of dogs. He found that the extravascular readings were always higher than the intravascular, although the error was not great. He determined that when a pressure equal to the intravascular minimum is put on the artery (as with the Riva-Rocci cuff) the maximum arterial pressure always increased. This made it difficult to obtain intravascular and extravascular pressures which were exactly comparable. The average error for the maximum (systolic) pressure varied from 3 to 5 mm. of mercury. The minimum intravascular and extravascular pressures practically correspond, because a pressure equal to the intravascular minimum does not affect the blood pressure. When cuffs narrower than 10 cm. were used, both the maximum and minimum extravascular pressures were far in excess of the intravascular.

Kolls[27] also compared direct and indirect methods in dogs. He had a cannula with a maximum and minimum valve in the one femoral artery and a cuff on the other femoral artery. The criterion for systolic pressure was the spreading of the limbs of the pulse tracing and for the diastolic pressure, the sudden decrease in amplitude. In six such determinations, the maximum difference between direct and indirect did not exceed 5 mm.

The work of Erlanger and of Kolls is valuable because the maximum and minimum valve measures the same changes in pressure as the cuff, namely, the maximum and minimum pressure.

In Man: Müller[28a] compared direct readings obtained with an elastic manometer and indirect readings (according to the method of von Reck-

26. Backmann, Louis: Sur la mesure de la pression artérielle chez les animaux, Compt. rend. Soc. de biol. **79**:338, 1916.

27. Kolls, A. C.: An Indirect Method for the Determination of Blood Pressure in the Unanaesthetized Dog, J. Pharmacol. & Exper. Therap. **15**:443, 1920.

28a. Müller, Otfried, and Blauel, Karl: Zur Kritik des Riva Rocci'schen und Gärtner'schen Sphygmomanometer, Deutsches Arch. f. klin. Med. **91**:517, 1907.

linghausen) in the radial arteries of patients whose arms were to be amputated. He found that the maximum pressure in both cases nearly corresponded. The indirect method gave readings from 8 to 10 mm. higher than those with the direct method. Dehon, Dubus and Heitz [28] obtained slightly higher results with a Riva-Rocci cuff on the brachial artery than with a cannula and an ordinary mercury manometer connected with the tibial artery. Volhard [29] came to a similar conclusion from his experiments. The use of the mercury manometer in the direct readings gives mean pressure only, which is not exactly comparable with the maximum and minimum pressures obtained with the Riva-Rocci cuff. For this reason, Merke and Müller [30] concluded that the experiments previously carried out on man should not be used as a criterion of the bloodless method of obtaining blood pressure. They themselves studied the blood pressure in two patients, one of whom had tumor of the brain and the other, tuberculous meningitis. They inserted a T cannula with a maximum and minimum valve into the brachial artery at the distal end of the bicipital fossa. They used a cuff 11 cm. wide for the indirect determinations. They concluded that it is possible to estimate exactly the maximum and minimum blood pressure with the bloodless method.

6. *Advantages and Uses of Indirect Method.*—The results of the more accurate of the foregoing experiments have established the fact that the indirect method can give satisfactory readings of systolic and diastolic pressure. The method has two main advantages: it does not require an anesthetic or operative intervention, and it can be repeated indefinitely. It does not replace the cannula method in any way, but is to be used for a different purpose. It is particularly valuable for prolonged experiments on animals.

7. *Indirect Methods in Use on Animals.*—The perfection of the indirect methods of determination of blood pressure on man and the ease of application have encouraged investigators to work out similar procedures suitable for animals. New methods have been published every few years, but the results have varied so much with different individuals that little of the work has been satisfactory. A review of the literature shows that the methods may be arranged in four groups: (*a*) readings on peripheral vessels with a tonometer; (*b*) readings on a central artery of a rabbit's ear; (*c*) readings on the carotids, and (*d*) readings on the aorta and femoral arteries.

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28. Dehon, M.; Dubus, A., and Heitz, Jean: Mesure directe de la pression intra-artérielle chez l'homme vivant, Compt. rend. Soc. de biol. **72**:789, 1912.

29. Volhard: Ueber die Messung des diastolischen Blutdruckes beim Menschen, Verhandl. d. Kong. f. inn. Med. **26**:200, 1909.

30. Merke, F., and Müller, Aloys: Experimentelles zur Hydromechanik und Haemodynamik, Ztschr. f. d. ges. exper. Med. **46**:332, 1925.

Tonometric: In 1899, Gärtner [14] made a practical use of Marey's original observation, the return of color to the skin with the release of pressure on the artery of supply. He named his instrument a tonometer. It is the first record of indirect measurement of blood pressure on an animal.

Apparatus.—The apparatus consists of (1) a pneumatic ring, made up of a metal ring 1 cm. high and 2.5 cm. in diameter, the inside of which is clothed with a rubber bag which can be filled with air; (2) a rubber bulb, and (3) a T tube uniting 1 and 2 with a mercury manometer.

The method is as follows: A finger is first made anemic by pushing it into a compression apparatus, such as immersion in mercury. The pneumatic ring is shoved over the second phalanx, and the pressure in it is raised to a point higher than the blood pressure. The compression apparatus is removed from the terminal phalanx, leaving it pale and bloodless. The pressure in the ring is gradually lowered, while the color of the finger is carefully observed. At the moment when the blood enters the pale part of the finger, coloring it purplish red, the pressure on the mercury manometer is identical with the blood pressure. Gärtner used this same principle to read blood pressures on the tails of dogs. In 1913, Trendelenburg [31] published a description of an application of the tonometric method on the fore leg of cats. Only cats with clear skin were suitable for use.

In 1916, Backmann [26] applied the method with slight modifications to rabbits. His apparatus was the same as Gärtner used.

According to this method, as the rosy skin of rabbits is normally hidden by long hairs, one of the posterior extremities is shaved. The distal part of the limb is rendered anemic by the application of a bandage. The pneumatic ring is applied above the bandage. The pressure is raised higher than the arterial pressure and is gradually lowered 5 mm. of mercury at a time. When the skin suddenly becomes red, the reading is taken. This indicates the normal blood pressure in the femoral artery. Backmann's figures for the normal averaged from 65 to 85 mm. of mercury. As many as thirty repeated observations in fifty minutes showed that blood pressure does not maintain an exact level. Comparison with the direct method gave almost parallel results when a cuff 25 by 18 mm. was used. The variations with different widths of cuffs were as much as 50 per cent of the pressure.

More recently, in 1922, van Eweyck and Schmidtmann [32] published a report of a tonometric method for use on rabbits. They stated that an observation of the capillaries of the skin is not possible even after the area is shaved. However, they found that the smallest vessels running in the fascia could be made visible and the rushing in of blood could be observed if a small opening (the size of a pea) were cut in the skin. They had difficulty in fitting the cuff on the conical thigh of the hind leg and could not obtain satisfactory results. For that reason, they used the fore leg.

31. Trendelenburg, W.: Ueber die Anwendung des Gaertnerschen Verfahrens der unblutigen Blutdruckmessung im Tierversuch, Ztschr. f. d. ges. exper. Med. **2**:1, 1913.

32. Van Eweyck, C., and Schmidtmann, M.: Zur Methodik der Blutdruckmessung beim Kaninchen, Virchows Arch. f. path. Anat. **236**:421, 1922.

The necessary apparatus consists of: a rabbit board; an India rubber bandage to produce the anemia; the tonometric cuff, to be fitted around the upper leg, and a manometer and rubber bulb with tubing and connections.

The rabbit is fastened on the board in the dorsal position. One of the fore legs is made anemic by means of the rubber bandage. The cuff connected with the bulb and manometer is placed around the upper leg. By inflation, the pressure is raised to about 160 mm. of mercury. The rubber bandage is unwound. A small incision through the skin is made with scissors at some point below the cuff. The pressure in the cuff is gradually released. At a definite level of mercury, the blood in the small arteries of the fascia streams in. A short time later, the borders of the wound begin to bleed. After the pressure is taken, the wound is closed by a suture and covered with iodine. Suppuration never takes place.

After taking many readings, van Eweyck and Schmidtmann concluded that the entrance of the blood from the wall of the wound is a more accurate criterion of the systolic pressure than the streaming in of blood in the vessels. They also found that accurate results can be obtained only if the pressure is allowed to fall slowly. It should take one minute to release 10 mm. of mercury. The readings must not be taken until the excitement produced by tying the animal has passed off. Consecutive readings give results within 2 mm. of one another. The average pressure in the fore leg of normal rabbits was from 90 to 100 mm. of mercury. Comparisons with the direct method were made in four animals, and the indirect readings corresponded with the minimal pressure.

Schönheimer,[33] using the procedure of van Eweyck and Schmidtmann, found the normal range to be from 80 to 112. Von Deicke[34] found the method fairly satisfactory, but felt that the necessary manipulation must influence the blood pressure. He did not have any difficulty with infection of the incisions in the skin. Thölldte[35] stated that his rabbits accustomed themselves to the manipulation with great difficulty.

The chief advantages of the tonometric methods of determinations of blood pressure are: (1) their simplicity; (2) the fact that they rely on one's most accurate sense, that of sight; (3) as many readings as desirable may be taken, and (4) anesthesia or operation is not necessary.

The disadvantages are numerous. 1. It is impossible to obtain both systolic and diastolic pressures. In any experiment in which blood

33. Schönheimer, Rudolf: Ueber die experimentelle Cholesterinkrankheit der Kaninchen, Virchows Arch. f. path. Anat. **249**:1, 1924.

34. Deicke, Otto: Beobachtungen an Kaninchen mit künstlicher Cholesterinzufuhr, Krankh. Forschung **3**:399, 1926.

35. Thölldte, M.: Hypercholesterinämie, Blutdruck und Gefässveränderungen im Tierversuch, Beitr. z. path. Anat. u. z. allg. Path. **77**:61, 1927.

pressure is of significance, it is equally important to have both maximum and minimum pressure.

2. In conditions of low pressure, the color does not return at all. In normal animals the flush may appear so gradually that it is impossible to get a reading. The time at which the flush appears depends partially on the rate with which the pressure is lowered. With too rapid lowering, there is an underestimation. Often with sufficiently slow release, a second deeper flush appears a few millimeters of mercury lower. Martin [18] found differences up to 20 mm. between the two flushes. This has been confirmed by other workers.

3. The vessels observed are small and are subject to vasomotor influence. At best, the results only indicate the pressure in the small peripheral arteries. Variations of pressure in these may be purely local and may not be any indication of the systemic condition. With successive determinations, the readings become higher and higher, more so than with the Riva-Rocci cuff. This may be due to continued compression, causing a vasomotor paresis.

4. Shapiro and Seecof [36] criticized the van Eweyck-Schmidtmann method because the struggling entailed in tying the rabbit to a board may increase its blood pressure. However, Schmidtmann stated that readings must not be taken until the excitement has disappeared. Shapiro and Seecof also suggested that the incision in the skin may influence the blood pressure in that limb by changing the blood flow to the part, and finally they point out how difficult it is for one person to watch the incision and note the blood pressure at the same time. The necessity for an assistant is certainly a disadvantage.

5. Perhaps the most obvious objection to the tonometric method is the lack of correspondence of results. Backmann's readings were taken on the posterior extremity of rabbits, while Schmidtmann's were taken on the fore leg. The vessels in these two areas must have almost the same blood pressure. Yet Backmann's figures for the normal were from 65 to 95 mm. of mercury, and Schmidtmann's were from 90 to 100 mm. of mercury. The fact that such reliable workers can obtain such different values with practically the same method speaks strongly against the use of a tonometer. The use of the tonometer in clinical practice has practically stopped, and it will probably meet with the same fate in experiments on animals.

Central Artery of Ear of the Rabbit: In 1906, von Recklinghausen [37] described a nonsurgical method for measurement of blood pressure in the ear of a rabbit.

36. Shapiro, Shepard, and Seecof, David P.: The Influence of Experimental Atherosclerosis upon the Systolic Blood Pressure in Rabbits, J. Lab. & Clin. Med. **10**:826, 1924-1925.

37. Von Recklinghausen, Heinrich: Unblütige Blutdruckmessung, Arch. f. exper. Path. u. Pharmakol. **55**:375, 1906.

Apparatus.—The apparatus consists of a flat inflatable rubber ring, shaped like a washer, and connected with a rubber bulb and a manometer; a glass plate; a spherical glass flask, such as is used in chemical laboratories (contents, about 15 cc.), and a watchmaker's lens.

The inner side of the ear lies against the flask. The hairy outside of the ear is shaved over the proximal portion of the central artery. On this the rubber bag with the hole in the center is placed so that the artery can be observed through the hole. A glass plate is applied over the rubber ring. The observation is carried out by means of the light through the lens. The course of the light is as follows: flask, inner side of ear, ear substance with vessels, outside of ear, hole through the rubber ring, glass plate, lens, eye of observer. The flask, ear and glass plate are held with the left hand, while the pressure in the bag is controlled with the right hand. An assistant reads the manometer. By varying the pressure in the rubber ring von Recklinghausen was able to see the vessel fill and empty. With a strong lens, he observed the course of single blood corpuscles and he could distinguish systolic and diastolic pressures.

Von Recklinghausen advised using a strong lens and only slightly pigmented animals. He noted the widening of the vessel in a warm room. The method does not seem to have been used much, chiefly because it was difficult to control the pressure applied. However, in 1923, Anderson [38] and Tohoru Kuraya [39] independently worked out and published modifications of von Recklinghausen's procedure.

Anderson's method is as follows:

Apparatus.—The apparatus consists of an especially designed U shaped pressure piece. One end is covered with a thin rubber membrane and connects with a mercury manometer and bulb. The other end contains a bright electric light such as is used in an ophthalmoscope. A lens is attached to the back of the pressure piece to magnify the vessel. The mercury manometer and bulb of rubber are used to make compression.

The rabbit's ear is slipped into the apparatus so that the proximal portion of the central artery lies between the rubber membrane and the source of light. When the light is on, pulsations may be observed in the vessel. As the pressure is raised, the pulsations cease. The level of mercury at which this occurs is taken as the systolic pressure.

Anderson stated that the readings must always be taken at the same point in the vessel since the pressure decreases peripherally. He found that excitation of any kind, even lifting the rabbit by the ears, gave an average rise of 13.3 mm. in pressure. Vasomotor changes altered the pressure; so he kept the ear covered with a small muff. External heat raised the pressure 20 mm. or more. He found that young rabbits tend to have a lower pressure than adults. His results were consistent. The average systolic pressure in the central artery of a rabbit's ear by this method varied from 76 to 87, with extremes of from 70 to 90. These figures were confirmed by Shapiro and Seecof [38] in their experiments on the influence of experimental atherosclerosis on the systolic blood pressure in rabbits.

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38. Anderson, Hilding C.: Demonstration of an Instrument for Taking Repeated Blood Pressures in Rabbits with Report of Some Experiments, Proc. Soc. Exper. Biol. & Med. **20**:295, 1922-1923.

39. Kuraya, Tohoru: A New Nonsurgical Method for Blood Pressure Measurement of a Rabbit with Special Reference to the Blood Pressure in Pericarditis, Acta scholae med. univ. imp. Kioto **6**:373, 1924.

In the same year, Tohoru Kuraya [39] published a report of a similar method.

Apparatus.—The apparatus consists of a glass plate, a rubber drum and a manometer.

Procedure.—The ear of the rabbit is shaved and the reading is taken in a warm room to dilate the vessel. An anesthetic is given to keep the animal motionless. The inner surface of the ear is placed next to the glass plate and the outer surface is in contact with the rubber drum which is connected with a manometer. The blood stream is stopped by raising the pressure in the drum. As the pressure is released, the blood streams through. This level of mercury is equal to the maximum or systolic pressure. An electric light may be attached to assist in observing the vessel. The blood pressure in the central artery of the ear in normal rabbits varies from 35 to 50 mm. of mercury. It is always from 56 to 63 mm. lower than the carotid pressure.

It is to be noted that Anderson's figures for the normal were from 75 to 90, while Kuraya's were from 35 to 50. The lower figures may have been obtained from a more distal part of the artery.

In 1926, Behrens [40] published a report of a similar method which he had worked out and used in 1923 independently of Anderson and Kuraya.

Apparatus.—The apparatus consists of a glass plate, a rubber membrane stretched over an artery and a Mareyscher glass case which is connected with a rubber bulb and a manometer.

The ear is placed in the small apparatus between the glass plate and the rubber membrane. The pressure is raised, and the ear is pressed against the glass plate. The central artery and vein are clearly visible. As the pressure increases, the vein disappears and only the pulsations in the artery can be seen. The reading is taken at the point at which the pulse disappears. His values for the normal, about 40 mm. of mercury, agree with those of Kuraya and so were probably taken on the same portion of the artery. Behrens pointed out that the chief disadvantage is due to the small size of the artery of the ear. External stimuli could cause such marked vascular constriction that a reading of blood pressure would be impossible.

In 1926, Watson [41] published another modification of von Recklinghausen's method. The principle is the compression of the central artery of the rabbit's ear by a rubber membrane attached to a pressure chamber on an illuminated stage. The pressure chamber is connected with a mercury manometer and bulb. The artery is observed through a lens focused on the stage. Watson's figures for the normal correspond with those of Anderson and Shapiro and Seecof.

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40. Behrens, A.: Zur Methodik der unblutigen Blutdruckmessung beim Kaninchen, Arch. f. d. ges. Physiol. **212**:372, 1926.

41. Watson, E. M.: A Method for Estimating Blood Pressure in Rabbits, J. Lab. & Clin. Med. **12**:706, 1927.

The advantages of the method of von Recklinghausen or any of its modifications are: (1) its simplicity and the ease with which numerous readings may be taken; (2) its dependence on the observer's visual sense. The disadvantages are: (1) the figures for the normal rabbit, quoted by Anderson and Kuraya, do not agree, although Anderson's results have been confirmed by several workers (Shapiro and Seecof); (2) there is the same objection to readings on the central artery as there is to those taken with a tonometer. Changes in pressure in such peripheral vessels may be local only (due to vasomotor influence) and not indicative of general blood pressure. In spite of the use of ear-muffs or a room of constant temperature, it is difficult to control the caliber of the vessel.

Carotid Tube: In 1911, van Leersum[25] reported an ingenious method for taking the blood pressure of rabbits. He selects young animals and performs an aseptic operation under ether anesthesia, thereby isolating and placing the carotid artery within a skin tube. Two longitudinal parallel incisions, from 7 to 10 cm. long and about 3 cm. apart, are made in the neck. The skin between the incisions is freed from the underlying muscle. The carotid artery is isolated from its surrounding structures for several centimeters. The edges of the skin are sewed together, enclosing the carotid artery in the tube thus formed. The outer edges of the two incisions are then sewed together. The incisions should heal by first intention, and the stitches may be removed within a week.

A rubber cuff 1 cm. wide and from 3 to 4 cm. long is connected by rubber tubing to an air pump and a manometer.

Procedure.—An assistant holds the rabbit, keeping the feet in one hand and the head in the other. The narrow rubber cuff is then wrapped around the carotid tube. Air is forced into the cuff until the artery is occluded, and then the pressure is gradually released. A finger on the carotid tube distal to the cuff palpates the first pulse wave that comes through. A second assistant at a signal notes the level of mercury and records that as the systolic pressure. In this way, from three to five readings a minute can be taken.

Van Leersum advises that readings be taken as soon after the operation as possible. The manipulation promotes the absorption of inflammatory products. If readings are not taken for six weeks the tube becomes hard and stiff. The procedure should be carried out in a quiet room, and the animal should be handled gently. The first few compressions of the tube exert a massaging effect and soften the skin so that less pressure is necessary to close the vessel. In excitable animals, these first readings are always higher than those which follow. It is advisable to disregard all values obtained until the animal is quiet and the tube softened. Van Leersum's figures for the normal carotid pressure are around 130 mm. of mercury. He compared his method with readings obtained with a cannula in the carotid and also in the femoral artery. The direct values for the femoral artery were 10.7 per cent lower and for the carotid,

10.4 per cent lower. This difference can be accounted for by the type of mercury manometer used, which records only mean pressure, while his indirect method records maximum pressure. The advantage of the van Leersum technic is that it is applied to an artery of medium size. The values obtained should therefore indicate the general blood pressure of the animal.

Van Leersum himself points out the main disadvantage of his method. The thickness of the wall around the artery alters the amount of pressure required to close off the column of blood. For that reason, he was surprised not to find greater variations between the direct and indirect methods. If this carotid tube could be isolated without altering the compressibility of the arterial wall by inflammatory reactions, the procedure would be more reliable.

The fact that an operation must be performed is in itself a disadvantage. Even if the wound heals, the artery may become thrombosed. After healing, the artery is in an exposed position and is always subject to trauma. This may result in hemorrhage, and the animal's usefulness for determinations of blood pressure is past. The necessity for two assistants hampers the procedure and leads to inaccuracy.

In 1920, Cohn and Levy [42] reported a modification of the van Leersum method. They used the same procedure, but they added to the apparatus. They have a graphic method of recording the pressure. The system between the cuff and the manometer is filled with water. The record is made on smoked paper by a writing point supported on a float on the mercury column. The criteria for maximal and minimal pressures used by Erlanger are utilized. The advantage of this method is obviously its greater accuracy. The substitution of the writing point for palpation of the pulse wave is certainly to be recommended. However, an increase in the amount of apparatus certainly does not simplify the method.

In 1924, Dominguez [43] published another modification of the van Leersum technic. The same operation is performed to obtain a carotid tube.

Apparatus.—The apparatus consists of a cuff 1.5 cm. wide, made of soft surgical drainage tubing, and a Riva-Rocci mercury manometer.

Procedure.—The rabbit is placed in a box with its head through an opening in front. The animal cannot slip in or out; so an assistant is not necessary. The cuff is placed around the carotid loop and fastened with a bulldog clamp. The readings are taken as in the original van Leersum method.

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42. Cohn, Alfred E., and Levy, Robert L.: A Modification of van Leersum's Bloodless Method for Recording Blood Pressures in Animals, J. Exper. Med. **32**:351, 1920.

43. Dominguez, R.: The Systolic Blood Pressure of the Normal Rabbit Measured by a Slightly Modified van Leersum Method, J. Metabol. Research **6**:123, 1924.

Dominguez reported blood pressures on sixty-three animals, and from 50 to 6,000 observations on each. His routine for each animal consists of ten readings, the taking of its pulse and the record of the temperature of the room. This requires about five minutes. His results are carefully controlled with regard to the effect of taking food; the effect of taking food after inanition; the effect of hemorrhage and the effect of injections of morphine. His figures for normal carotid pressure in rabbits vary from 90 to 150. He compared his method with the pressure obtained from a cannula in the femoral artery. His readings averaged 18 mm. higher. When he used a maximum and minimum manometer in the other carotid artery, his readings were only from 10 to 12 mm. higher. He concluded that the method gives the real values of blood pressure with sufficient accuracy to render comparable the results obtained from day to day.

The advantage of the Dominguez modification lies in the fact that one person only is required to make the observations. The disadvantages depend on the complications of the operation which he himself reports. The skin flap often becomes necrotic. The scar tissue contracts and obliterates the artery. When infection occurs in the loop, the artery often becomes thrombosed. There was a 20.8 per cent mortality rate in a series of ninety-six operations; twenty-one more animals could not be used on account of necrosis or infection. Thus, 57 per cent of the operations were successful. This is a high mortality rate at the beginning of the experiments without considering the accidents in which the carotid loop may later be involved.

In 1926, Behrens [40] reported still another modification of the van Leersum technic. The carotid loop is obtained by the usual operation.

Apparatus.—The apparatus consists of a glass tube, from 8 to 10 mm. in diameter, with a hookshaped attachment on one end for the reception of the carotid. At one end of the tube is a thin rubber membrane which on inflation lies against the hookshaped process and pinches off the carotid. The apparatus has exactly the principle as that of Anderson, which was used on the rabbit's ear. The rest of the apparatus consists of a rubber bulb and mercury manometer.

The apparatus is applied as centrally as possible and at right angles to the loop so that the artery is not pulled from its natural position. The pressure is raised until the pulse in the carotid disappears. This is estimated by palpation. An assistant reads the manometer and records the pressure. Behrens gave the average carotid pressure in normal rabbits as 90 mm. of mercury. In same cases, it was as high as 120. Comparison with the cannula method gave a maximum error of 5 per cent. This method requires an assistant and does not have any particular advantage over the procedures of Dominguez or van Leersum.

Cuff: In 1904, Erlanger [17] succeeded in reading the blood pressure in the femoral artery of dogs by an indirect method.

Apparatus.—Erlanger's sphygmomanometer, which is the most accurate instrument of its kind obtainable was used. The width of the cuff is from 6.3 to 9 cm.

It was found that the application of the cuff to the conical shape of a dog's thigh was difficult. The cuff was dragged down on the leg as the pressure was raised, thus losing much of the force. To do away with this difficulty, the limb was made cylindric by excising muscles on the dorsal and ventral aspects of the thighs of large dogs. The excess of skin was removed and the wound allowed to heal. Cuffs of different widths were applied to the thigh. The systolic pressure was estimated by palpating the pulse in the femoral artery or by Erlanger's graphic method. The extensive operation involved in this procedure prevents its being a practical method.

In 1912, Theodore Fahr [44] reported a new technic for taking readings of blood pressure on rabbits

Apparatus.—The apparatus consists of a cuff of the Riva-Rocci type connected with a rubber bulb and a mercury manometer.

The cuff is wrapped around the abdomen of the animal. The pressure in it is raised until the abdominal aorta is occluded. The pressure is gradually released and by palpation of the femoral artery the first pulse wave is noted. This level of mercury is equal to the aortic systolic pressure. In their criticism of this method, Shapiro and Seecof stated that constriction of the rabbit's abdomen is unphysiologic. A more important and practical objection is the difficulty of palpating the femoral artery in so small an animal.

Janeway [45] reported a simple means of obtaining measurements of blood pressure on dogs.

Apparatus.—The apparatus consists of a modified Riva-Rocci cuff, one 7.5 by 15 cm. being used for large dogs and one 5 by 11 cm. for small dogs, and a pressure bottle connected with the cuff and manometer through valves operated by foot pedals. This leaves both hands free.

The cuff is wrapped around the lower fore leg. The pressure is slowly increased to above blood pressure. The obliteration of the pulse is palpated at the artery at the bend of the ankle or on the plantar surface of the paw. Janeway stated that it is impossible to palpate the return of the pulse after obliteration. Even obliteration of the pulse can be detected only in those dogs with a large superficial artery. When the animal is quiet, the pressure can be read with a maximum error of 15 mm. on the side of underestimation.

This appears to be a simple method which is applicable for the larger laboratory animals. An operation is not required, and the dog need not be tied. The only difficulty, then, is the palpation of the peripheral vessel. Janeway overcame this by careful selection of the animals.

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44. Fahr, Theodore: Beiträge zur experimentelle Atherosklerose unter besonderer Berücksichtigung der Frage nach den Zusammenhand zwischen Nebennierenveränderungen und Atherosklerose, Verhandl. de deutsch. path. Gesellsch. **15**:234, 1912.

45. Janeway, T. C., and Edwards, A. Park: An Experimental Study of the Resistance to Compression of the Arterial Wall, Proc. Soc. Exper. Biol. & Med. **5**:156, 1907-1910.

In 1920, Kolls [27] published a report of an indirect method of determination of blood pressure on dogs.

Apparatus.—After carefully studying the shape of a dog's thigh, Kolls devised a specially shaped cuff. For dogs weighing from 6 to 14 kg., the cuff is 14 cm. wide. For larger dogs, a longer and wider cuff must be used. He devised a special instrument to record the pulsations, because the ordinary sphygmograph was not delicate enough.

The part of the cuff which is inflexible and of sheet aluminum is placed over the external surface of the thigh. Pressure is applied over the internal surface, thus compressing the femoral artery. The cuff does not tend to be dragged distally; so pressure is not lost in that way. Comparison with the direct method, a maximum and minimum valve cannula in the opposite femoral being used, gave differences not exceeding 5 mm. This procedure is particularly valuable for use on dogs. It does not depend on palpation, which is often so unsatisfactory. It would not be suitable for rabbits, but is the method of choice in larger animals.

Götze [46] used the ordinary cuff to obtain estimations of blood pressure on cattle. He applied the cuff to the tail of the animal, raised the pressure to above blood pressure and then gradually lowered it. By palpation of the coccygeal artery for return of the pulse, he obtained the systolic pressure.

In 1923, a report of another simple and accurate method for obtaining readings of blood pressure on dogs was published by Frederick Allen.[47]

An ordinary sphygmomanometer, with a cuff of the size used for infants, and a stethoscope with a phonendoscope bell piece, small and flat, about 2 cm. in diameter and 0.75 cm. thick, with a celluloid diaphragm, are used. There is a ring on each side to attach tapes.

The dog is kept in a standing position by a frame and canvas bands which pass under the abdomen. A strap holds the tail still. The lower part of the hind leg is shaved and the course of the femoral artery located. The stethoscope bell is attached by the tapes over the vessel. The cuff is wrapped around the leg so that the lower border just covers the stethoscope bell. Readings are taken as in clinical practice. The cuff is inflated until the pulse is obliterated. As the pressure is lowered, the first sound indicates the systolic, and the fourth phase, when the sound suddenly fades, is the diastolic, pressure. Observations are more easily obtained on animals that are accustomed to being handled. The sounds are usually clearer on larger dogs. The method has been used successfully on sheep. Allen's figures for the normal average 79 diastolic, 139 systolic, with a pulse pressure of 60 mm. Controls were made with a cannula and an ordinary mercury manometer, and there was a satisfactory parallelism between the readings. Allen's method, like that of Kolls, is dependable for dogs. In smaller laboratory animals, however, the sounds of the femoral vessels cannot be heard with a stethoscope.

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46. Götze, R.: Ueber indirekte Blutdruckmessungen an Haustieren insbesondere an Rindern, Berl. Tierärztl. Wchnschr. **26**:293, 1920.

47. Allen, Frederick: Auscultatory Estimation of the Blood Pressure of Dogs, J. Metabol. Research **4**:431, 1923.

Rabbits and dogs are probably the most commonly used laboratory animals. In experiments which last for several months, it is necessary to have an indirect method of determination of blood pressure to take daily readings. For dogs, the methods of both Kolls and Allen are simple and accurate. They are superior to a direct method because they do not require an anesthetic or an operation. They are better than the other indirect procedures because they do not depend on palpation of a small peripheral artery.

For rabbits, blood pressures may be taken most easily by the Anderson or by the van Leersum methods. The possibility of vasomotor influences detracts from the reliability of pressures taken on the central artery of the ear. The carotid tube of van Leersum would seem to be the most satisfactory procedure if it were not for the high operative and postoperative mortality rate. Tonometric methods are possible but are certainly not dependable. It is evident, then, that to date there is no simple accurate means of indirectly measuring a rabbit's blood pressure.

A NEW METHOD FOR TAKING REPEATED READINGS OF BLOOD PRESSURE

My purpose in this paper is to report a new method for taking repeated readings of blood pressures on rabbits and other laboratory animals. The procedure is simple and accurate. It does not require an operation or an anesthetic. It is really a combination of the methods of Allen and Fahr.

Apparatus.—The apparatus consists of an inflatable cuff 12 cm. wide connected with a rubber bulb and a mercury manometer, such as is used routinely in clinical work; a stethoscope of the phonendoscope type with a flat bell 3 cm. in diameter and 0.75 cm. deep, with a celluloid diaphragm (tapes may be attached to small side handles), and a rabbit board (figs. 1 and 2).

Procedure.—The rabbit must be tied on its back. It is important that this be accomplished without any struggling or excitement on the part of the animal. It is possible to obtain that result by observing in detail the following technic. Place the animal on its four feet on the board. Tie a cord about 18 inches (45.7 cm.) long to each hind leg above the knee joint so that it will not slip off. Fasten the strap which is attached to the upper portion of the board around the rabbit's body behind the shoulders. The strap must fit snugly, but not tightly enough to interfere in any way with breathing. Holding firmly and steadily on the pelvic girdle, turn that portion of the animal on its back. The head and front legs, although above the strap, will also rotate. Tie the cords attached to the rabbit's hind legs to the clips on the board. With a little practice, a rabbit can be tied down in the supine position without causing it any discomfort. The animals soon accustom themselves to the procedure and do not offer any objection. The cuff is next wound around the rabbit's abdomen, so that its inferior border is just above the crest of the ilium (fig. 2). It is important that this fit snugly. The phonendoscope bell is slipped under the lower border

of the cuff in the midline. In this way it lies over the termination and bifurcation of the abdominal aorta (fig. 1). Some difficulty may be encountered because the phonendoscope may not remain in position. If so, the tapes on its borders may be loosely attached to clips on the board.

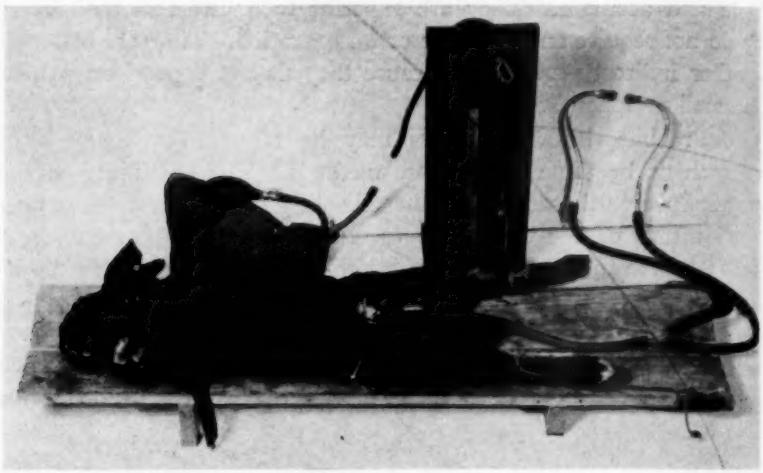

Fig. 1.—Appearance of apparatus, position of rabbit and position of phonendoscope.

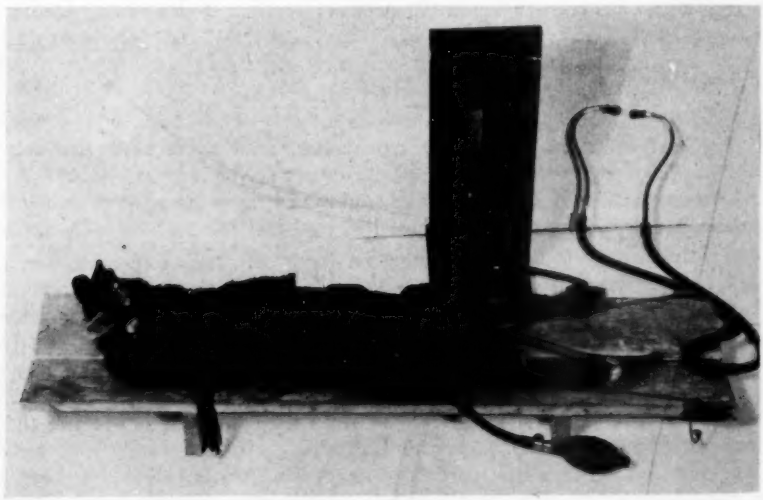

Fig. 2.—Appearance of apparatus in place ready for reading of blood pressure. The phonendoscope is just under the lower border of the cuff.

Readings are taken exactly as in clinical procedures. The cuff is inflated until the aorta is obliterated and the pressure is gradually released. The sounds are loud and clear. The first sound indicates systolic and the fourth diastolic pressure.

Precautions.—It is essential that the rabbit be tied down without any struggling. This is easily accomplished with a little practice. If the animal has resisted and has become excited, it should be tied securely and left to lie quietly for at least five minutes.

It is convenient to use two rabbit boards. One animal is tied down and the apparatus adjusted. While it lies there, a second animal is tied on the

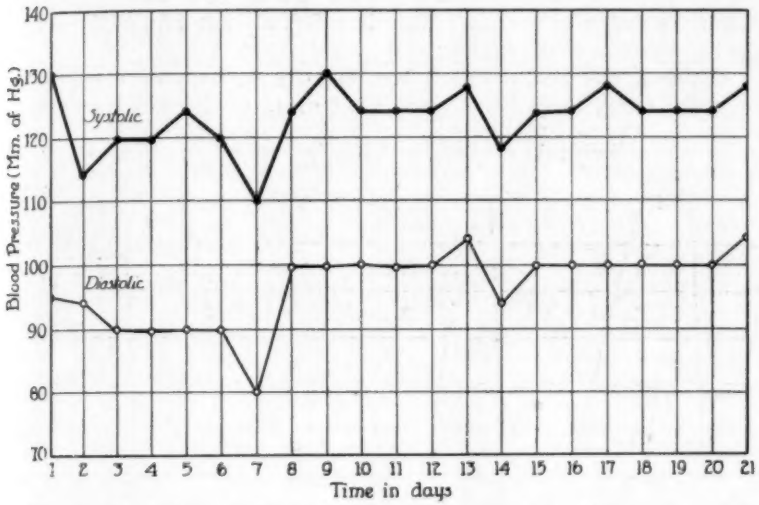

Fig. 3.—Variations in blood pressure of a normal rabbit over a period of twenty-one days.

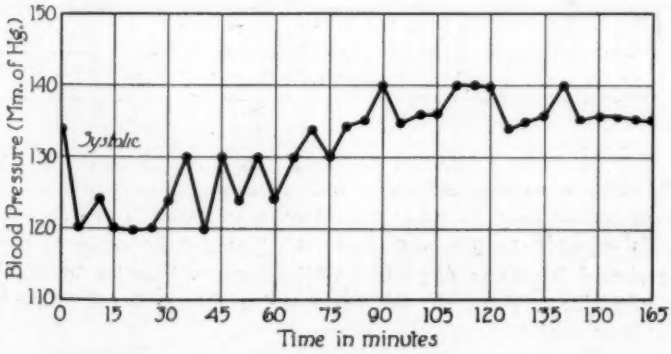

Fig. 4.—Variations in systolic blood pressure of a normal rabbit at five minute intervals over a period of 165 minutes.

second board. Readings are then taken on the first rabbit. The apparatus is transferred to the second rabbit. A third is tied to the first board. In this way time is saved, and each animal has time to become relaxed.

It is important that the phonendoscope is not more than covered by the lower border of the cuff or the readings will be higher.

The cuff must be 12 cm. wide. During the development of the method, different widths of cuffs were tried. The values obtained with a 5 cm. cuff were 50 mm. higher on a normal rabbit and almost 100 mm. higher on experimental animals with hypertension. The abdomen of the average rabbit is almost the circumference of an adult's arm, and the aorta is about the size of the human brachial artery. It is evident, then, that a 12 cm. cuff is required.

As in clinical procedure, the pressure should be lowered very gradually. Otherwise, the readings will be underestimated. On the other hand, it is necessary to work as rapidly as possible so that the rabbit will not struggle, because of prolonged constriction of the abdomen.

The routine in this laboratory has been to raise the pressure in the cuff to 200 mm. at least four times. The mercury is lowered to zero each time without

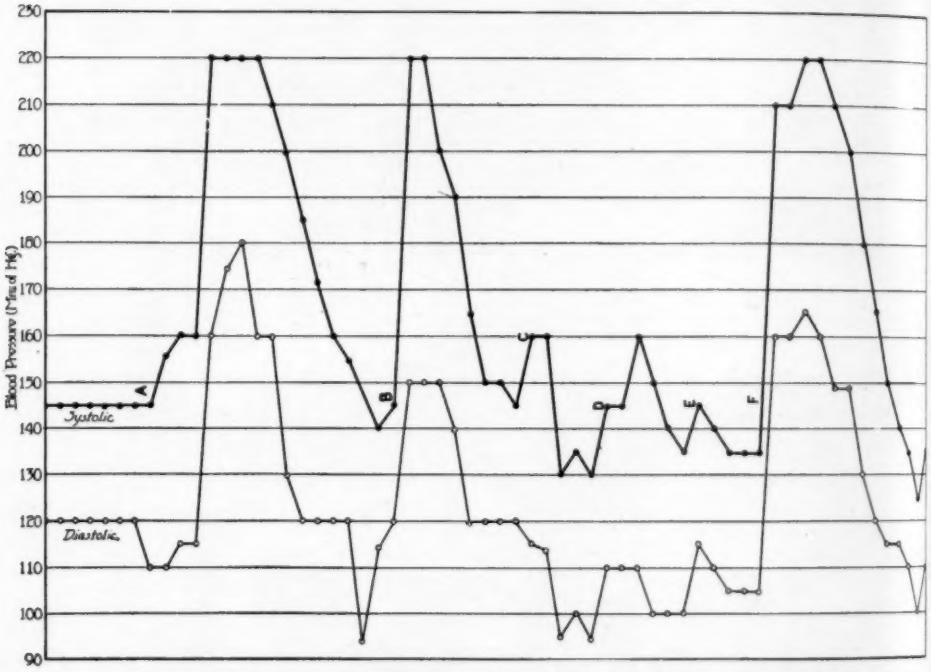

Fig. 5.—Blood pressure of normal rabbit showing (*A*) effect of intramuscular injection of 1 cc. of 1:1,000 epinephrine; (*B, C, D* and *E*) effect of repeated massage at site of injection; (*F*) effect of intravenous injection of 0.5 cc. of 1 per cent ephedrine sulphate. In this figure and in figures 6 and 10, the blood pressure readings were taken every two minutes.

any oscillation. The first reading is discarded. It serves to relax the abdominal musculature. The next three readings are averaged. They seldom vary more than 5 mm. and never more than 10 mm. The blood pressure does not rise with successive readings. If there is a difference, the first reading is usually higher. There is often some muscular resistance to the first constriction on each occasion, but there seems to be none thereafter.

If there is any struggling or excitement on the part of the rabbit, the readings are discarded and the procedure repeated in five or ten minutes.

Disadvantages.—The method cannot be used advantageously immediately after certain operations on the abdomen. It is necessary to wait two days or more to allow time for healing. The constriction of the abdomen may cause rupture of the surgical wound or may be so painful that the rabbit struggles. It has, however, been satisfactory two days after operation on the kidneys, such as nephrectomy, experimental hydronephrosis or ligature of renal vessels. The right kidney is normally located above the area of constriction. The left kidney is so movable in the abdominal cavity that it slips up above the cuff while the pressure is being taken.

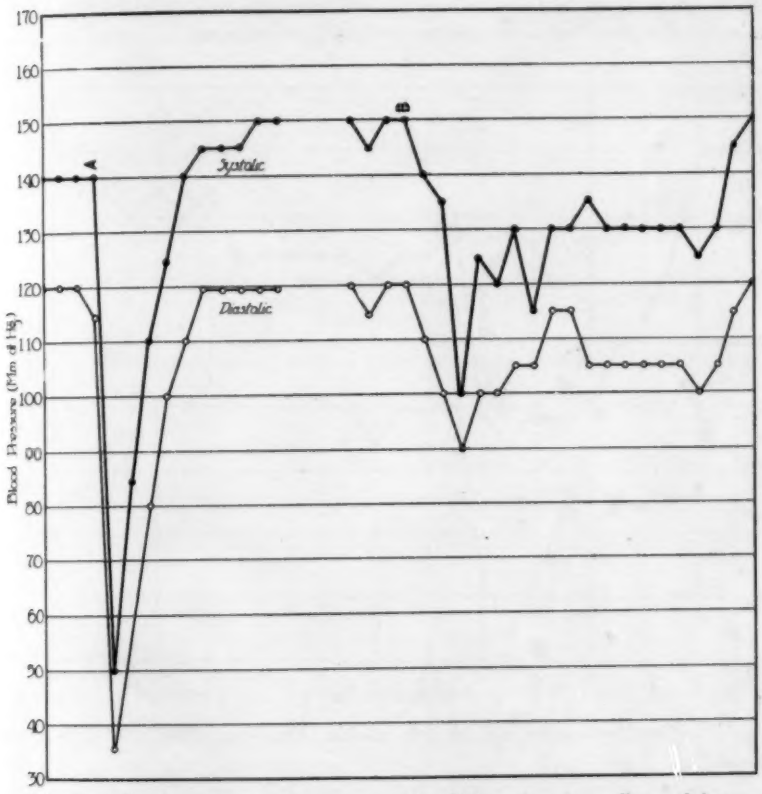

Fig. 6.—Blood pressure of two normal rabbits, showing effect of intravenous injection of 0.001 Gm. of acetylcholine (*A* and *B*).

Advantages.—An anesthetic is not required; operation or trauma of any kind is not necessary; the animal is not hurt, and so there is no struggling or resistance; the apparatus is the same as that used clinically and therefore is easily available, and the criteria are the same as those in clinical practice and the sounds are loud and clear.

Normal Readings of Blood Pressure.—The average of 1,120 readings of blood pressure on eighty-four normal rabbits is systolic pressure, 125, diastolic pressure, 90. The most extreme systolic figures obtained were 160 and 90. These were never encountered in any one animal. The average normal variation in systolic pressure in a rabbit is never more than 25 mm. and rarely more than 20 mm.

Figure 3 is a graphic record of daily readings of blood pressure on a normal rabbit, covering a period of twenty-one days. It shows fluctuations of 20 mm. in the three weeks. Figure 4 represents readings of systolic blood pressure taken every five minutes for almost three hours. This animal shows extremes of 120 and 140 mm. pressure in that time.

Experiments Showing the Use of This Method.—Experiments with drugs were undertaken because it was felt that these should test the accuracy of the method. The usual pharmacologic effects were obtained and the results are shown. Typical curves were obtained from intravenous injection of 1 cc. of a 1 : 1,000 solution of epinephrine. Generally the pressure rose to about 210 within five minutes and then fell below normal within forty minutes. It often remained

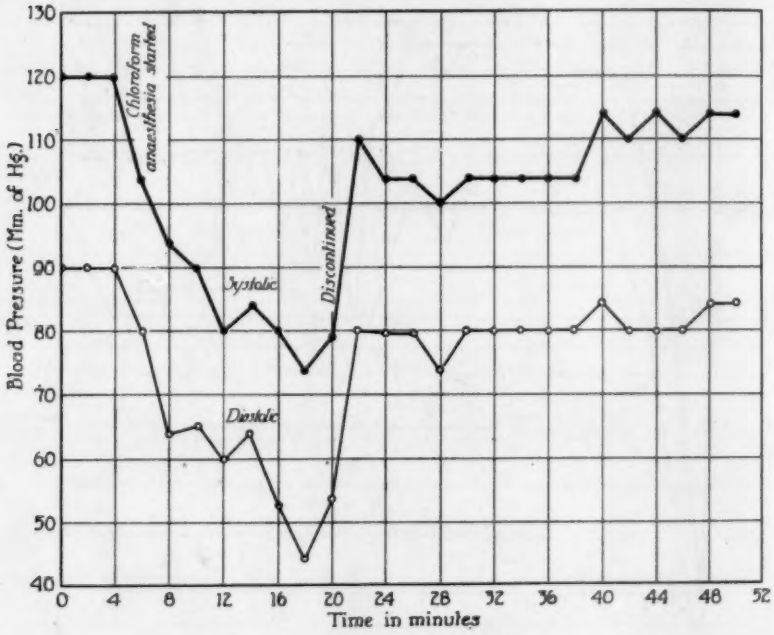

Fig. 7.—Blood pressure of normal rabbit, showing effect of chloroform anesthesia.

below normal for from one to four days, in accordance with the experiments of van Leersum. Occasionally, when it was given subcutaneously, the epinephrine did not cause any change in pressure until the area of injection was massaged.

In figure 5, the epinephrine was injected into the muscles of the thigh, and a rise of blood pressure was obtained. When the pressure fell to normal, the thigh was massaged and a second rise was obtained. The massaging was continued until it did not have any effect. Then ephedrine was injected intravenously. The pressure rose at once, giving a typical epinephrine curve.

Figure 6 shows the lowering of pressure which resulted when acetylcholine was given intravenously. The pressure fell lower in the first rabbit but soon returned to normal. The pressure remained low for a longer time in the second rabbit.

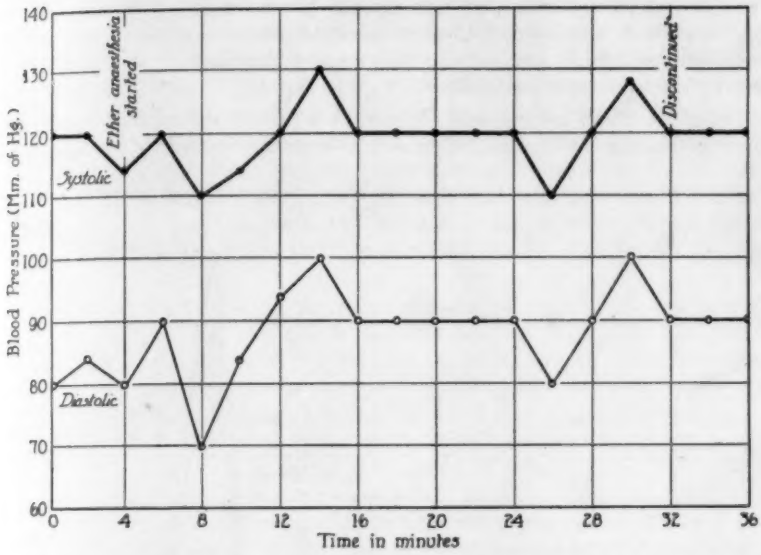

Fig. 8.—Blood pressure of normal rabbit, showing effect of ether anesthesia.

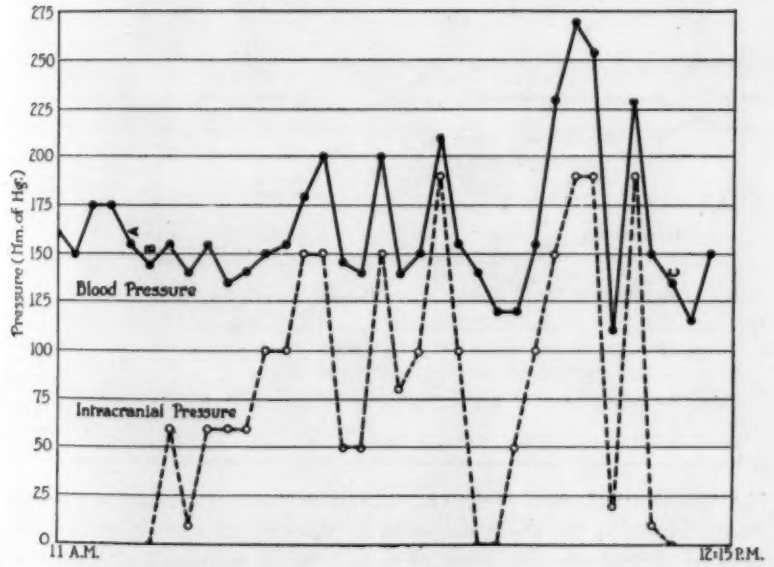

Fig. 9.—Blood pressure of normal rabbit, showing effect of increased intracranial pressure, according to Cushing's experiment. See text. *A* indicates beginning of anesthetic; *B*, insertion of cannula and *C*, end of experiment.

Figure 7 shows the effect of chloroform anesthesia on blood pressure. The fall was almost instantaneous, as was the rise when the inhalation was discontinued. Figure 8 illustrates the effect of ether anesthesia. The fluctuations obtained were within 20 mm. of one another and therefore do not differ from normal variations in that time period.

Effect of Increased Intracranial Pressure.—A part of the original experiment of Harvey Cushing [48] was repeated to demonstrate the regulatory mechanism of

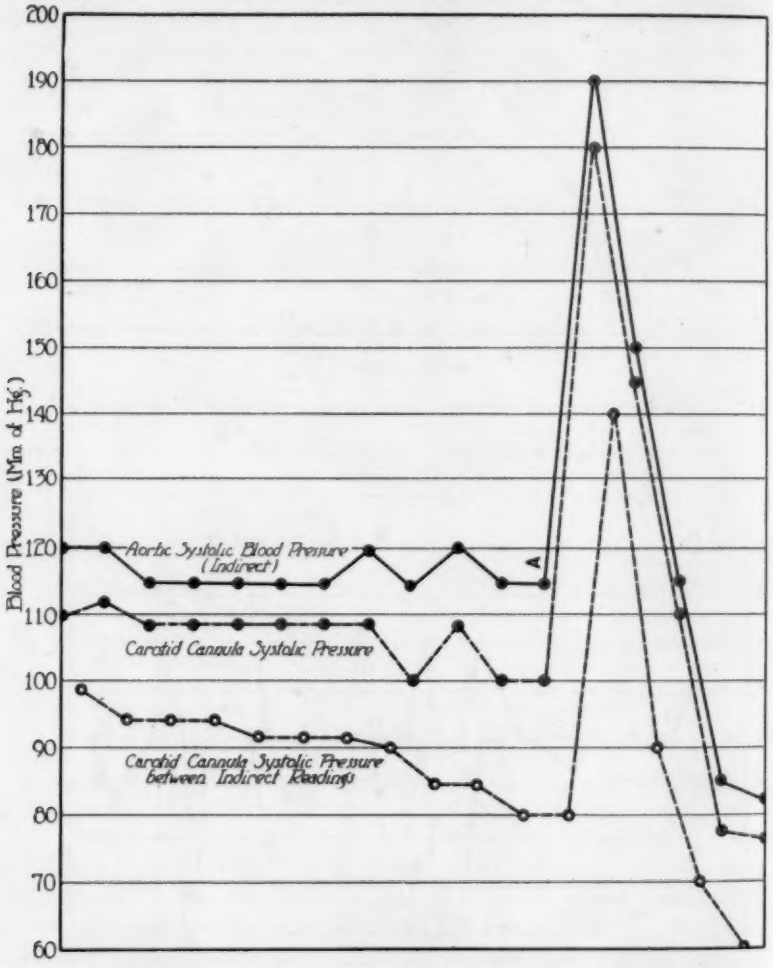

Fig. 10.—Comparison of direct and indirect methods of taking blood pressure. The compression of the abdominal aorta by the indirect method raises cannula readings of carotid pressure from 10 to 15 mm. of mercury. *A* indicates the intravenous injection of epinephrine.

48. Cushing, Harvey: Concerning a Definite Regulatory Mechanism of the Vasomotor Center which Controls Blood Pressure During Cerebral Compression, Bull. Johns Hopkins Hosp. **12**:290, 1901.

the vasomotor center which controls blood pressure during cerebral compression. A general compression of the brain was produced by physiologic sodium chloride solution at body temperature being forced into the cerebrospinal space through a cannula. Figure 9 shows that the normal blood pressure for this rabbit varied between 150 and 175. With the animal under ether anesthesia, the intracranial pressure was gradually raised, beginning at zero. Until intracranial pressure reached 150, i. e., about the level of systolic pressure, there was no rise in blood pressure. At that point the blood pressure rose to 200, because a medullary anemia was produced which stimulated the vasomotor center. The systolic pressure of 200 was sufficient to overcome the intracranial tension. When the latter was raised to 185, the blood pressure rose to 270.

During the next week, in the course of another experiment, this animal had its celiac ganglions removed. After the abdominal wound healed, the experiment in intracranial tension was repeated. The same rise in blood pressure was obtained.

Comparison with Method Using an Ordinary End Cannula.—With the animal under ether anesthesia, an ordinary end cannula, mercury manometer and kymograph were connected with the carotid artery of a rabbit (fig. 10). The blood pressure cuff and phonendoscope were placed in position so that aortic readings could be taken. The uppermost line in figure 10 represents aortic blood pressure taken by the indirect method. The middle line represents simultaneous readings of carotid pressure obtained with the cannula. The lower line represents cannula readings of carotid pressure obtained between the taking of the aortic pressures. The graph shows an average difference of 10 mm. between the direct carotid reading and the indirect aortic reading. The graph also illustrates how the constriction of the abdomen which is used in the indirect method raises the general blood pressure from 15 to 20 mm. This rise is only temporary and is lost as soon as the pressure in the cuff is released. Clinically, also, compression of a limb raises the systemic blood pressure from 5 to 20 mm., depending on the length of time the compression is maintained. Janeway[45] explained the rise as due to a central vasomotor reflex which increased the peripheral resistance. Figure 10 also illustrates the effect of epinephrine. The blood pressure curves by the direct and indirect methods parallel one another. It would be desirable to obtain simultaneous indirect and direct aortic readings. This is impossible, because the cannula would lie under the cuff around the abdomen.

Comparison with Method Using Maximum and Minimum Valve Cannula.—These experiments showed that the systolic reading with the cannula averaged 5 mm. lower than the aortic reading with the cuff. It is probable that carotid maximum pressure is 5 mm. lower than aortic maximum pressure. In that case the indirect reading with the cuff practically corresponds to the aortic maximum pressure as obtained with the cannula.

COMMENT

Until recently, all readings of blood pressure on animals have been obtained by means of a cannula. It is still the method of choice for many types of experiments. Within the last few years, reports of a great many indirect procedures have been published. With the exception of the methods of Kolls and Allen, which are satisfactory but which can be used only on dogs, there are two main objections to all the other procedures. They require complicated apparatus which

the investigators must learn to use, or else some operative intervention is necessary. This new method is offered because it has neither of these disadvantages. The apparatus is exactly the same as that used in clinical practice. The procedure is also the same. A 12 cm. cuff must be used, and the animal must be allowed to relax for several minutes before the reading is taken. All the sounds are the same as those heard in the human brachial artery. They are loud and clear.

The results parallel those obtained by the direct method. The indirect aortic pressure is about 10 mm. higher than the simultaneous reading of the direct carotid pressure, an ordinary end cannula being used. The indirect aortic pressure is only 5 mm. higher than the simultaneous carotid reading with a maximum valve. However, aortic pressure is probably about 5 mm. higher than carotid pressure. Therefore, the results obtained by this indirect method are equal to the intravascular aortic pressure at the moment the reading is taken. They are from 15 to 20 mm. higher than the intravascular aortic pressure between the taking of the readings. The same factor applies clinically. It is well known that pressure on one brachial artery raises the general blood pressure. This new method is particularly valuable for use on rabbits in prolonged experiments when the animals must be kept alive. The procedure does not cause excitement when conducted with care. Repeated readings may be taken, and neither operative intervention nor anesthesia is required.

SUMMARY

1. All references in the literature to the indirect methods of obtaining readings of blood pressure on laboratory animals are reviewed.

2. A new indirect method for taking repeated aortic systolic and diastolic readings on rabbits is presented. The method is particularly simple and easy, because the apparatus and criteria are identical with those used clinically.

Values of aortic blood pressure for normal rabbits are given. The average of 1,120 readings on eighty-four normal rabbits is: systolic pressure, 125; diastolic pressure, 90. When this method is used, the administration of epinephrine, and ephedrine and increased intracranial pressure cause a typical rise, while acetylcholine and chloroform cause a fall in blood pressure.

General Review

STATUS LYMPHATICUS

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NEW YORK

In 1614, Felix Plater [1] reported the sudden death without adequate cause of a boy, aged 5 months; at necropsy, the most prominent abnormality noted was an enlarged thymus. He also referred to the occurrence of sudden death in two other boys in the same family who had similar symptoms. Thus, more than 300 years ago, two of the most prominent features of status lymphaticus were recognized. From this time the association of sudden death with enlarged thymus in cases of laryngeal stridor, asthma and acute respiratory obstruction was more frequently reported, notably by Morgagni and Bichat, but no serious attempt appears to have been made to bring the thymus into causal relationship with the clinical symptoms until 1830, when Kopp [2] advanced the view that laryngospasm was a true thymic asthma due to the pressure of an enlarged thymus on the trachea, great vessels or autonomic nerve trunks. The thymus thus became the central feature, and Kopp's physical explanation was generally accepted until 1858, when Friedleben [3] published his classic experimental and clinical studies on the thymus. He denied that pressure from an enlarged thymus could explain Kopp's "asthma thymicum," and briefly expressed this view in his well known dictum "Es gibt kein asthma thymicum." Friedleben's conclusions were based on a vast amount of experience, both with the clinical and pathologic aspects and with experiments in the physiology of the thymus. Many of his conclusions are still sound, as, for example, that the thymus may be congenitally absent or experimentally removed without detectable impairment of health, and that it may have an obscure influence on the nutrition of the osseous system.

After Friedleben's work, other important contributions to the subject were not made until the work of Arnold Paltauf [4] in 1889. Paltauf supported Friedleben's conclusions that the enlarged thymus was a secondary factor in thymic asthma. From a study of the large material available to him as coroner's physician in Vienna, he advanced the

1. Plater, F.: Observationum in hominis affectibus pleurisque, alvi tres, Basileae, 1614.

2. Kopp, J.: Oenkwürdigkeiten in der ärztlichen Praxis, Frankfurt-a.-M., 1830, vol. 5.

3. Friedleben, A.: Die Physiologie der Thymus-Inise, Frankfurt-a.-M., 1858, p. 366.

4. Paltauf, A.: Wien. klin. Wchnschr. **2**:877, 1889; **3**:172, 1890.

theory that "thymus death" was due to a lowered resistance dependent on a specific constitutional anomaly of a lymphatic-chlorotic type which so weakened the influence of the nervous system that persons with this anomaly were unable to withstand shocks or injuries which would not have seriously affected normal persons. The anatomic changes observed, he believed, were only the gross manifestations of the nutritional defect or anomaly which he designated status lymphaticus.

TERMINOLOGY

Many terms are still in common use to designate this specific constitutional defect. Among the more common ones are: laryngismus, asthma thymicum (Kopp), stridor thymicus, mors thymica, status lymphaticus or constitutio lymphatica, status thymicolymphaticus, status thymicus and status hypoplasticus.

Many clinicians and pathologists who recognize the existence of a specific-constitutional defect still treat these names as indicating slightly, or distinctly, different pathologic states. I do not believe there is any basis for this separation at present. All the facts indicate that these terms are descriptive of the different degrees, the different manifestations and the different stages of fundamentally the same physiologic defect occurring at different ages. The tendency to split up status lymphaticus into several component parts, while perhaps unavoidable in the formative period of knowledge concerning this defect, has the effect of introducing confusion and even hindering the acquisition of new facts. In this review, therefore, I shall use the term "status lymphaticus" or "constitutio lymphatica" of Paltauf as the least prejudiced term for this constitutional defect. The term status lymphaticus, while it is also a misnomer, has the advantage of eliminating the thymus from the title rôle—a position it has occupied for more than 300 years—at the same time emphasizing the most prominent anatomic characteristic. Status hypoplasticus is a more inclusive and more easily misused term.

DEFINITION

Status lymphaticus may be defined as a constitutional defect, usually congenital (though it may be acquired), dependent on an inadequacy of some function of the suprarenals, sex glands and autonomic nervous system, and associated with lowered resistance or increased susceptibility to a great variety of nonspecific, physical and chemical agents. Anatomically, it is characterized by delayed involution or hyperplasia of the thymus, hypertrophy and hyperplasia of the lymph glands and lymphoid tissue of the various organs, underdevelopment of the chromaffin, gonadal (suprarenal cortex, interstitial cells of testes and ovaries) and cardiovascular systems and certain peculiarities of external configuration.

ANATOMY AND PHYSIOLOGY OF THE THYMUS

As the thymus is still considered by many as the central feature of status lymphaticus, a summary of the anatomy and physiology of this organ may be helpful in evaluating its importance in the essential and more detailed manifestations of this constitutional defect.

Anatomy.—The thymus gland develops as paired structures from the entoderm of the third and fourth gill arches in close association with the corresponding parathyroids. The anlagen from the fourth arch remain rudimentary in most mammals.

According to Hammar,[5] the epithelial character of the thymus is evident until the end of the second month of intra-uterine life. At this stage, the cells become more loosely arranged and give off protoplasmic processes which anastomose to form the reticulum. Concerning the further development whereby the gland becomes a complex lymphoid-like tissue at the height of its development, divergent views are still held. The theory supported by Koelliker,[6] Beard,[7] Stoehr,[8] Bell[9] and Schridde[10] assumes that the fully developed thymus and all its essential components arose from the original epithelium by repeated divisions and modifications of form.

The theory at present most popular, which was developed largely by His,[11] Stieda,[12] Hammar[13] and Maximow,[14] claims that the reticulum and Hassall's corpuscles are the only elements developed from the original epithelial anlage while the small thymic cells (lymphocytes) and eosinophils arise from mesenchymal cells that have migrated into the epithelial structure from surrounding tissues, and that further development of the thymus is that of a true lymphoid tissue.

In support of the view that the small thymic cells are true lymphocytes are the facts that these two types of cell resemble each other in their morphologic characteristics, in their susceptibility to roentgen-ray injury, in their serologic reactions, in having ameboid movement and in their general pathologic behavior. Despite these resemblances to true lymphoblastic tissue, there is still a basis for doubt.

Gross Morphology.—The fully developed thymus is roughly triangular, with the base resting on the pericardium. Anatomists have clearly

5. Hammar, J. A.: Anat. Anz. **27**:23 and 41, 1905.
6. Koelliker, A.: Entwicklungsgeschichte des menschen, ed. 2, Leipzig, 1879.
7. Beard, J.: Zool. Jahrb. **17**:403, 1903.
8. Stoehr, P.: Anatomische Hefte, Wiesbaden **31**:409, 1906.
9. Bell, E. T.: Am. J. Anat. **5**:29, 1906.
10. Schridde, H.: Centralbl. f. allg. Pathol. u. path. Anat. **33**:284, 1923.
11. His, W.: Ztschr. f. wissensch. Zool. **11**:164, 1881.
12. Stieda, F.: Leipzig, 1881, p. 38.
13. Hammar, J. A.: Arch. f. Anat. u. Physiol., Anat. Abteil., 1907, p. 83.
14. Maximow, A.: Arch. f. mikr. Anat. **79**:560, 1912.

shown that breathing during the first days of life materially alters the shape of the thymus from a broad triangular form before respiration is established to an elongated triangular form. Despite the effort expended, the only standard as to normal or abnormal which has been established is size in relation to age, and, as Hammar [15] has frequently emphasized, this is of little value unless the actual parenchyma is measured. With so crude a standard, the data available are necessarily conflicting because of the great variability due to age, to pathologic involution, to varying degrees of the "lymphatic constitution," to geographic and climatic factors (especially districts in which goiter is prevalent) and differences of race (Chinese, Shellshear [16]).

The most commonly quoted average weights of the thymus in relation to age are shown in the following table.

Average Weight of Thymus in Relation to Age

	Weights of Thymus in Grams				
Age	Friedleben 1858	Von Sury 1908	Hammar 1906	Schridde 1923	Bratton 1925
Newborn	14	14	13	13	11
1- 5 yrs.	1-9 mos. = 20	22	23	17	24
	9 mos.-2 yrs. = 26				
6-10	3 yrs.-14 yrs. = 26	29	26	20	29
11-15	..	32	38	25	27
16-20	15-25 yrs. = 22	..	26	20	..
21-25	..	..	25	19	..
26-35	3	..	20	14	..
36-45	..	..	16	10	..
46-55	..	..	13	7	..
56-65	..	..	16	4	..
66-75	..	..	6	3	..

These compilations may be taken as representative of numerous others. Age and pathologic involution have been excluded in Hammar's figures. On the other hand, his figures may be high because of this, or because mild cases of status lymphaticus are included, and there is no means of excluding this factor.

Anatomists in general agree that the absolute weight of the thymus increases rapidly up to the end of the second year of life and then changes but little until the seventh year, when it again increases slightly to fall off again about the eleventh year. According to Bratton,[17] the weight of the thymus in relation to body weight increases for a part of the first six months of life, then decreases rapidly. Relative to sex, the thymus is larger in the male during the first four years of life; it remains approximately equal in the two sexes until the eleventh year, after which it is larger in the female.

15. Hammar, J. A.: Ztschr. f. Ang. Anat. **1**:311, 1914.
16. Shellshear, J. L.: China M. J. **38**:646, 1924.
17. Bratton, A. B.: J. Path. & Bact. **28**:609, 1925.

Age Involution.—By age involution is meant the normal atrophy of the thymus in man and in animals, which sets in at the age of puberty and continues through old age. Waldeyer [18] (1890) first showed that widely separated strands of thymic tissue consisting largely of reticular cells are normally found in the thymic area throughout life; he thus disposed of a prevalent view that the thymus completely disappears in old age. There are no definite distinguishing features between the age involution and the pathologic or accidental involution due to disease. The two types of involution may occur simultaneously, and accidental involution followed by regeneration must occur in most persons one or more times before the normal involution sets in. If one excludes the stroma, the parenchyma of the thymus ordinarily reaches its maximum weight about the end of the second year in man, and then remains more or less stationary until puberty when an abrupt decrease sets in. Hammar stated that the increase in the size of the gland after the second year is largely due to the increase in the interlobular stroma.

Why sexual maturity should mark the turning point in the size of the thymus is unknown. Some have claimed that the sex glands play a decisive rôle in initiating this anatomic and physiologic decline of the organ. There is abundant evidence that the cause is a far more complex culmination of the interactions of the glands of internal secretion, and at least involves the thyroid, suprarenal and sex glands. After sexual maturity, there is rapid reduction in the volume of the parenchyma for the first four or five years; then the reduction becomes more and more gradual. This reduction in volume is due largely to a decrease in the small thymic cells. The mechanism of the decrease in the number of lymphocytes is not understood. The decrease in volume of the medulla occurs later; it is in part due to a decrease in the rate of division of the reticular cells and in part to their actual disintegration. New reticular cells, new Hassall's corpuscles and new small thymic cells are being formed during involution, and according to Hammar,[15] all the elements are being formed throughout life, though at a greatly reduced rate. In the normal involution, there is usually only a slight increase in the intralobular connective tissue, though a true sclerosis of the lobule may occur in association with congenital syphilis and exhaustion atrophy (Warthin [19]).

Accidental or Pathologic Involution.—Accidental or pathologic involution differs from normal involution in that it occurs rapidly and at any age. It is seen in all animals and apparently under a great variety of conditions, such as acute and chronic infections, various intoxications, acute and chronic inanition, following roentgen-ray injury and during

18. Waldeyer, W.: Sitzungsb. d. k. preuss. Akad. e. Wissensch. **25**:433, 1890.
19. Warthin, A. S.: Arch. Pediat. **26**:597, 1909.

pregnancy. All these conditions, in some unknown way, cause a massive migration and destruction of the small thymic cells. The disintegrated small thymus cells are ingested in huge quantities by the reticular cells. The gland may shrink to one fifth of its previous weight within a week. The medulla also decreases, but never to the extent that the cortex does. According to Hammar,[5] Jonson [20] and others, Hassall's corpuscles are relatively increased but absolutely decreased, and in extreme degrees of accidental involution they disappear.

Regeneration may occur rapidly after pathologic involution; it also occurs within eight or ten days in thymic autografts. The most characteristic feature of regeneration in the rat is the rapid proliferation of reticulum followed by the appearance of small thymic cells in about five days.

Physiology.—The function of the thymus is unknown. It closely resembles the lymphoid tissues in its principal physiologic and pathologic reactions, and most students associate it with those tissues. There is no proof that it has an internal secretion. The hypothesis of Svehla [21] is without supporting evidence. The fact that the thymus exists throughout life and undergoes physiologic involution; that during starvation, acute infections and intoxications it undergoes an acute involution; that in certain conditions such as status lymphaticus and after gonadectomy in early life its normal involution is delayed, and that under other conditions as in exophthalmic goiter, acromegaly, Addison's disease and following suprarenalectomy, it may regenerate—all indicate that it plays some important rôle in the maintenance of normal nutrition, at least during the period of growth up to sexual maturity. The results of extirpation as first shown by Friedleben on dogs and goats prove that the organ is not essential to life. In more recent times, the extirpation experiments of Hammar [22] and Vincent [23] on frogs, of Tarulli and LoMonaco [24] and Park and McClure [25] on dogs, of Park,[26] Paton and Goodall [27] and others on guinea-pigs, of Pappenheimer [28] and others on rats, of Marine and Manley [29] and Van Allen [30] on rabbits, have

20. Jonson, A.: Arch. f. mikr. Anat. **73**:390, 1909.

21. Svehla, K.: Wien. med. Bl. **19**:723, 740, 757, 775, 791, 806 and 821, 1896.

22. Hammar, J. A.: Arch. f. d. ges. Physiol. **110**:337, 1905.

23. Vincent, S.: J. Physiol. **30**:XVI, 1904.

24. Tarulli, L., and LoMonaco, D.: Bull. d. r. Acad. med. di Roma **23**: 311, 1897.

25. Park, E. A., and McClure, R. D.: Results of Thymus Extirpation in Dog, Am. J. Dis. Child. **18**:317 (Nov.) 1919.

26. Park, E. A.: J. Exper. Med. **25**:129, 1917.

27. Paton, D. N., and Goodall, A.: J. Physiol. **31**:49, 1904.

28. Pappenheimer, A. M.: J. Exper. Med. **19**:319, 1914.

29. Marine, D., and Manley, O. T.: J. Lab. & Clin. Med. **3**:48, 1917.

30. Van Allen, C. M.: J. Exper. Med. **43**:119, 1926.

confirmed and extended Friedleben's conclusions that thymectomy is usually not followed by detectable symptoms.

On the other hand, Basch,[31] working with young puppies, believed that fairly characteristic symptoms appeared after a latent period of from two to three weeks. He recorded defective ossification, fragility of the skeleton and hypersensitiveness of the peripheral nerves as the most prominent symptoms, and he believed that this symptom complex was in some way related to rickets. He concluded, however, that the gland was not indispensable to life, but exercised an important influence in promoting the growth and calcification of bone. Soli [32] concluded from his work on thymic extirpation in hens that this gland was concerned in the normal metabolism of calcium. He also noted that after a latent period of from two to four weeks thymectomized hens laid eggs of smaller size and with imperfectly calcified shells. Klose and Vogt [33] extended and confirmed the observations of Basch. They, too, recognized a latent period of from two to four weeks in puppies before the appearance of impaired calcification, stunting and weakness, which they designated "cachexia thymopriva" and which eventually led to death from "coma thymicum" in from two to fourteen months. The results of Basch and Klose are obviously not correct. The difficulties of complete removal, the occurrence of infection and the presence of accessory thymic tissue have undoubtedly been factors in the results reported, but it cannot yet be stated that thymectomy is without effect.

Brieger, Kitasato and Wassermann [34] found that thymus extract diminished the virulence of bacteria and neutralized their toxins. Similar effects were obtained with lymph gland extracts. Hammar also believed that the thymus exercises a detoxifying effect in common with the lymph glands rather than that it produces an internal secretion.

Barbára [35] expressed the view that the thymus forms substances (opsonins) that stimulate phagocytosis, and, in addition, either forms complement or stimulates other organs to produce it. There is abundant evidence that the lymphoid tissues in general are intimately concerned in the formation of antibodies. The observations of Také and Marine [36] that suprarenalectomized rabbits, and of Jaffe and Marine [37] that suprarenalectomized rats, may form antibodies as well as or more rapidly than normal animals, although the resistance of such animals to toxins is greatly reduced, have been associated by these investigators with the

31. Basch, K.: Wien. klin. Wchnschr. **16**:393, 1903.
32. Soli, U.: Arch. ital. de biol. **52**:353, 1909.
33. Klose, H., and Vogt, H.: Beitr. z. klin. Chir. **69**:1, 1910.
34. Brieger, L.; Kitasato, S., and Wassermann, A.: Ztschr. f. Hyg. **12**:137, 1892.
35. Barbára, M.: Societa Editrice Libraria, Milano, 1918, p. 1-260.
36. Také, N. M., and Marine, D.: J. Infect. Dis. **33**:217, 1923.
37. Jaffe, H. L., and Marine, D.: J. Infect. Dis. **35**:334, 1924.

regeneration of the lymph glands and thymus which follows suprarenalectomy. So also the observation of Tanabe [38] that Japanese soldiers with status lymphaticus, although they react severely to injections of typhoid vaccine, produced as high agglutinin titers as normal persons may be interpreted as involving a thymic factor.

The effect of feeding thymus and of the injection of extracts have yielded little information of value. Gudernatsch [39] reported that feeding thymus delayed the metamorphosis of tadpoles. Romeis [40] and Abderhalden [41] have confirmed this observation. Uhlenhuth [42] ascribed this effect to the inadequate diet. E. R. Hoskins [43] and Downs and Eddy [44] did not obtain any effects by feeding thymus to rats and rabbits. Riddle [45] observed a group of doves and pigeons which, on the diet used, produced soft shelled eggs deficient in albumin. He further found that the administration of 20 mg. of dried ox thymus daily corrected this defect.

Chemically, nothing significant has been found except that Bang [46] reported that thymic tissue yields as much as five times the quantity of nucleic acid that lymph glands do.

All observers agree that the thymus is an important source of blood lymphocytes and possibly of eosinophils (Badertscher [47]). There is a close parallelism between the number of lymphocytes in the peripheral blood and the activity of the thymus. That red blood cells are formed in the thymus at any period is still doubtful, although this view is strongly supported by Badertscher.

Interrelations.—The most outstanding physiologic features concern the interrelations of the thymus with the sex glands, the thyroid and the suprarenals. Calzolari [48] showed that the removal of the testes in young rabbits delayed involution of the thymus. This observation has been confirmed many times (Henderson,[49] Goodall,[50] Gellin,[51] and Marine, Manley and Baumann [52]).

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38. Tanabe, B.: Mil. Surgeon **52**:92, 1923.
39. Gudernatsch, J. F.: Am. J. Anat. **15**:431, 1914.
40. Romeis, B.: Arch. f. mikr. Anat. u. Entwicklungmech. **104**:273, 1925.
41. Abderhalden, E.: Arch. f. d. ges. Physiol. **211**:324, 1926.
42. Uhlenhuth, E.: J. General Physiol. **1**:305, 1918.
43. Hoskins, E. R.: J. Exper. Zool. **21**:295, 1916.
44. Downs, A. W., and Eddy, N. B.: Endocrinology **4**:420, 1920.
45. Riddle, O.: Am. J. Physiol. **68**:557, 1924.
46. Bang, I.: Beitr. z. chem. Physiol. u. Path. **5**:317, 1904.
47. Badertscher, J. A.: Anat. Record **18**:23, 1920.
48. Calzolari, A.: Arch. ital. de biol. **30**:71, 1898.
49. Henderson, J.: J. Physiol. **31**:222, 1904.
50. Goodall, A.: J. Physiol. **32**:191, 1905.
51. Gellin, O.: Ztschr. f. exper. Path. u. Therap. **8**:71, 1911.
52. Marine, D.; Manley, O. T., and Baumann, E. J.: J. Exper. Med. **40**: 429, 1924.

Gonadectomy does not cause hypertrophy of the thymus. Reports to the contrary, I believe, are due to other factors (suprarenal and thyroid). Suprarenalectomy in rabbits (Marine, Manley and Baumann) and in rats (Jaffe [53]), not only prevents involution, but may cause regeneration of the highly involuted thymus provided the thyroid gland is intact. On the other hand, thyroidectomy hastens involution in rabbits (Jeandelize, Lucien and Parisot,[54] and Marine, Manley and Baumann [52]) as well as prevents the regeneration of the thymus which ordinarily follows suprarenalectomy. Hammett [55] found that thyroparathyroidectomy in rats markedly reduces the growth of the thymus. Fulci [56] and Henderson [49] observed that pregnancy also hastens involution. R. G. Hoskins,[57] Utterstrom,[58] Kahn,[59] Courrier [60] and others have noted that feeding of thyroid extract causes enlargement of the thymus. Positive evidence has not been made out of an interrelationship with the spleen (Mann and Marine, Manley and Baumann), with the pituitary or with the parathyroids. On the basis of the close embryologic relationship of the thymus and parathyroids, a functional connection would appear possible, and it happens that most of the alleged effects of thymectomy are related to calcium metabolism and impairment of ossification. The fact that thymus remnants undergo hypertrophy in young animals after removal of the major portion of the thymus also indicates a functional need for this tissue. Friedleben and Basch noted this, and although frequently denied, it has been clearly demonstrated by Gottesman and Jaffe [61] in rats.

PATHOLOGIC ANATOMY

I accept the view expressed by Friedleben, Paltauf, Wiesel,[62] Hart,[63] Ohlmacher,[64] Thomas [65] and others that there is not a known disease entity in which the thymus occupies the central or causal rôle. The terms "thymus death," thymic asthma, status thymicus, status thymicolymphaticus are misleading. On the other hand, I believe that status lymphaticus

53. Jaffee, H. L.: J. Exper. Med. **40**:325 and 619, 1924.
54. Jeandelize, P.; Lucien, M., and Parisot, J.: Compt. rend. Soc. de biol. **66**:942, 1909.
55. Hammett, F. S.: Am. J. Anat. **32**:53, 1923.
56. Fulci, F.: Centralbl. f. allg. Pathol. u. path. Anat. **24**:968, 1913.
57. Hoskins, R. G.: Am. J. Physiol. **26**:426, 1910.
58. Utterstrom, E.: Arch. de méd. expér. et d'anat. path. **22**:550, 1910.
59. Kahn, R. H.: Arch. f. d. ges. Physiol. **163**:384, 1916.
60. Courrier, R.: Compt. rend. Soc. de biol. **84**:226, 1921.
61. Gottesman, J. M., and Jaffe, H. L.: J. Exper. Med. **42**:413, 1925.
62. Wiesel, J.: Virchows Arch. f. path. Anat. **176**:103, 1904.
63. Hart, C.: München, J. F. Bergmann, 1923, p. 172.
64. Ohlmacher, A. P.: Ref. Handb. Med. Sc., N. Y. **18**:179, 1917.
65. Thomas, E.: Jena, Gustav Fischer, 1927, p. 84.

or status hypoplasticus is a clinical and pathologic entity the chief physiologic characteristic of which is lowered resistance and in which hypertrophy and hyperplasia of the lymphoblastic tissues is a frequent anatomic manifestation. Recently, Greenwood and Wood [66] asserted that the term status lymphaticus is a good example of the growth of medical mythology, and that it was as accurate to attribute the cause of death to "the visitation of God" as to status lymphaticus. These authors seem to have laid too great stress on the thymus and overlooked the essential feature of Paltauf's conception. It is of secondary importance whether the thymus is large or small, since the thymic change indicates only the stage or degree of the individual's lymphoid reaction at the time.

If it is assumed that status lymphaticus is a nutritional defect or deficiency disease tending toward spontaneous recovery and manifesting itself at different ages, it follows that there are all degrees of the condition, mild and severe, and all stages, progressive and regressive. With such a conception, it is readily understandable that a constant morbid anatomy cannot be present any more than the thyroid changes could be constant in all stages of goiter. If, however, one allows for the range, the stage and the age, it is hardly to be doubted that a striking similarity of lesions is found in a significant number of persons who die more or less suddenly from apparently trivial causes. The lesions observed are body-wide and their relative importance cannot yet be evaluated. For the present, one must be content with cataloging them in the order of their prominence and constancy, and necessarily much must be omitted that may be of the greatest significance in the tissues whose capacity for objective manifestations is below the threshold of detectability by the present methods.

Thymus.—The thymus gland is usually found to be larger than it should be for the particular age of the individual. Size and weight, however, must be controlled by a microscopic determination of the amount of lymphoid tissue present. If examined at the height of its capacity for regeneration as occurs in early childhood, the parenchyma may be two or three times the normal average size, and weights of from 60 to 80 Gm. are frequently seen and occasionally up to 135 Gm. On the other hand, Warthin [19] and others have described cases in which the thymus was sclerotic from exhaustion atrophy. One must assume from analogy with the thyroid that the exhaustion atrophy of the thymus was preceded by a full lymphoblastic differentiation. Others have shown that accidental involution from one cause or another may temporarily or permanently reduce an enlarged thymus. Age involution (i.e., partial recovery, status lymphaticus recessivus of Symmers [67]) of the thymus

66. Greenwood, M., and Wood, H. M.: J. Hyg. **26**:305, 1927.
67. Symmers, D.: Am. J. M. Sc. **156**:40, 1918.

and lymph glands may occur in these cases, and must be kept in mind. Hammar [68] expressed the prevailing opinion that there is no essential histologic difference between the usual thymus of status lymphaticus and that of a normal child. Schridde,[69] however, believed that hyperplasia of the medulla is fairly characteristic, while the cortex may be atrophic or of normal thickness. At the height of the thymic hyperplasia, germinal centers as described by Wegelin [70] may occur.

Spleen.—The spleen is usually moderately enlarged, often to such a degree that it may be palpated. The malpighian bodies are prominent. When associated with rickets, there is usually a mild grade of interstitial fibrosis and an increase in blood pigment in the pulp. The endothelial elements have been found hyperplastic.

Lymph Nodes.—Lymph glands show wide differences in the degree of enlargement and also regional differences independent of age. The lymph nodes most prominently involved are the pharyngeal, thoracic and abdominal chains. Hypertrophy of the lymphoid tissue of the nasopharynx (adenoids) is usually present. The lingual and faucial tonsils are nearly always enlarged, and Schridde [71] lays great stress on hypertrophy of the lingual lymphoid tissue as being of clinical diagnostic importance.

The newly formed lymphoid tissue at the height of its reaction may form a diffuse infiltration of the pharyngeal mucosa extending into the epiglottis. The cervical, axillary and inguinal lymph glands may be palpably enlarged. The mesenteric, and particularly the intestinal, lymph nodes are usually strikingly enlarged. Focal necrosis of the germinal centers has been described by Symmers and others as characteristic of status lymphaticus. It is not constant. The Peyer's patches and solitary follicles may be prominent. Microscopically, the appearance is that of simple hyperplasia with active germinal centers. Occasionally fibrosis and exhaustion atrophy of the lymph nodes are present. This indicates the end-stage of an ineffectual compensatory hypertrophy. Collections of lymphoid cells are found in several organs, as, for example, the liver, kidneys, the skeletal muscles (lymphorrhagia) and particularly the thyroid. The bone marrow often shows changes. Red marrow may occur in the shafts of the long bone, and a diffuse or focal lymphoid replacement may be present. Hedinger [72] and others have described the occurrence of true lymph nodes with germinal centers in the bone marrow.

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68. Hammar, J. A.: Ztschr. f. Kinderh. **13**:218, 1915.
69. Schridde, H.: München. med. Wchnschr. **71**:1533, 1924.
70. Wegelin, C.: Centralbl. f. allg. Pathol. u. path. Anat. **29**:441, 1918.
71. Schridde, H.: München. med. Wchnschr. **59**:2605, 1912.
72. Hedinger, E.: Jahrb. f. Kinderh. **63**:308, 1906.

The view that the thymus and lymph glands are complementary tissues has been suggested by Marfan and Warthin as a possible explanation of the fact that hypertrophy of the thymus may be present with the lymph nodes and spleen fibrotic, or both the thymus and lymph glands may be hyperplastic or the lymph nodes may remain hyperplastic after involution of the thymus.

Reticulo-Endothelial System.—Few studies have been made with Aschoff's system particularly in mind. Aschoff [73] is inclined to view the entire lymphoid hyperplasia as a specific reaction of the reticulo-endothelial system. In experimental status lymphaticus produced in rats, Scott has described plugs of endothelial leukocytes in the capillaries of the lungs. Marine and Deutch [74] have been unable to show that the number of tissue mast cells were notably altered in suprarenalectomized rats. In view of the relation of the lymphoid and hematopoietic tissues to the defensive mechanism of the body (phagocytosis, antibody formation, etc.), it seems that further studies on the reticulo-endothelial system offer a good prospect for additional data on the nature of status lymphaticus.

The Thyroid Gland.—The thyroid gland is frequently slightly enlarged even in regions in which goiter is uncommon, and it is almost constantly enlarged in cases reported from districts in which goiter is prevalent. The stroma of such glands is usually somewhat increased, indicating a prolonged struggle, and the gland at the time of examination may be actively hyperplastic or involuted. There is abundant experimental evidence that the thyroid is intimately associated with the thymus and lymphoid tissue. (This association is explained in the section of physiology). Apart from the physiologic antagonism which those data indicate, the significance of thyroid enlargement in status lymphaticus is unknown. I have seen the idea that status lymphaticus may be endemic like goiter mentioned in the literature but once (McNeil and McGowan [75]). The more frequent occurrence of status lymphaticus in districts in which goiter is prevalent is mentioned by Ohlmacher.

Suprarenals.—It has been known for a long time that the suprarenals may be small, but Wiesel was the first to point out that the chromaffin tissue as well as the cortex may be strikingly reduced. Hedinger has reported similar occurrences. Warthin observed it only in a small proportion of his cases. The cortex may or may not be decreased. Wiesel would associate this hypoplasia of the chromaffin system with the cardiovascular changes, the low blood pressure and the increased vagus tone characteristic of status lymphaticus. He would also assume a close

73. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924.

74. Marine, D., and Deutch, M.: Studies on the Distribution and Possible Function of Tissue Mast Cells, Arch. Path., Soc. Tr. **4**:321 (Aug.) 1927.

75. McNeil, C., and McGowan, J. P.: Edinburgh M. J. **10**:201, 1913.

relationship between status lymphaticus and Addison's disease; this view is further supported by the experimental production of status lymphaticus by Crowe and Wislocki [76] in dogs, by Marine, Manley and Baumann in rabbits, and by Jaffe in rats.

Since suprarenalectomy performed on rats and on rabbits causes a lowering of resistance and thymic regeneration, it is probable that the spontaneous involution of the human suprarenal cortex, which begins during the second week of extra-uterine life, may be a causal factor in the hypertrophy of the thymus and lymph glands and the lowered resistance in infants. There is evidence of great variations in the degree of suprarenal involution, varying from a mild degenerative change in the fasicular layer to extensive hemorrhagic destruction of both the fasicular and reticular layers and ending fatally.

This destructive degeneration of the human suprarenal cortex apparently does not occur in animals, and it is possible that because of this status lymphaticus is rare in animals.

Sexual Organs.—As most fatal cases of status lymphaticus occur in children, morphologic changes in the sex glands would be difficult to recognize. In the majority of subjects examined after puberty, however, significant changes have not been observed. Kyrle and Symmers refer to a peculiar increase in the stroma of the testes in a considerable number of cases. Careful studies on the interstitial tissue have not been recorded, but in view of the relation of the suprarenal cortex to the disease, such studies might give data of importance. The ovaries of adults are sometimes larger and sometimes smaller than normal. They present a smooth surface owing to diminished formation of follicles and corpora lutea. Underdevelopment of the uterus has been noted frequently.

Cardiovascular System.—In the patients examined after puberty, hypoplasia of the heart and the large arteries has been prominently mentioned since Virchow [77] first called attention to the occurrence of this abnormality in the chlorotic and lymphatic constitution. Much was said about the lowered resistance of such persons depending on this circulatory anomaly. Symmers expressed the view that chlorosis was only an incidental and transient condition in girls with status lymphaticus. Schridde stressed a slight relative hypertrophy of the left ventricle. Wiesel showed that a similar hypoplasia of the cardiovascular system may be present in Addison's disease. Several writers have described a deficiency of the muscle fibers and elastic tissue in the artery walls in these cases, and rupture of such arteries has been reported. Myocardial disease and severe atheromatosis have also been noted in the late stages.

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76. Crowe, S. J., and Wislocki, G. B.: Bull. Johns Hopkins Hosp. **25**:287, 1914.

77. Virchow, R.: Beitr. z. Geburtsh. u. Gynäk. **1**:323, 1872.

The underdevelopment of the cardiovascular system may be primary, but in most instances it seems more logical to assume that it is secondary to the general asthenia and low blood pressure, and, as Hart has pointed out, does not appear to have any pathologic significance.

Nervous System.—Anatomic changes of note have not been described, although there is abundant evidence of serious functional derangement. Timme [78] has discussed the neuropsychiatric relations in status lymphaticus. In fact, the whole group of diseases with general lymphoid hyperplasia are intimately related to disturbance of function of the nervous system; for example, epilepsy, exophthalmic goiter, Addison's disease, myasthenia gravis and status lymphaticus. Emerson [79] pointed out that in 22 per cent of the cases studied the persons were mental defectives, and Symmers emphasized the emotional and nervous instability of persons with status lymphaticus.

Osseous System.—Disturbances in calcification have been prominently associated with status lymphaticus from the beginning. In cases of status lymphaticus occurring in infancy and childhood, a considerable portion of the patients show more or less pronounced evidence of rickets. In older persons so-called juvenile rickets and osteomalacia have been found in a significant number of cases. In 1893, Kundrat [80] pointed out that the changes in the bone in cases of rickets were but one of the manifestations of the basic vegetative dyscrasia or nutritional disturbance. Now that the pathogenesis of rickets is better understood as a deficiency disease, and in view of the close association with status lymphaticus, it seems that the work on rickets may indicate the direction research should take in the further study of the nutritional defect which underlies status lymphaticus, that is, there may be a vitamin insufficiency in addition to a hormonal insufficiency.

General Anatomic Changes.—The blood usually shows a relative lymphocytosis. This may be as high as 60 per cent of all leukocytes in children at the height of the reaction. The lymphocytosis is in general proportional to the prominence of the lymphoid tissue. Preservation of the fetal lobulations of the kidney is frequently mentioned, as is also the preservation of the infantile type of appendix and cecum. The velvety skin, the decrease in hair and the preservation of well developed subcutaneous fat may be mentioned.

Association with Other Diseases.—Markham first noted enlargement of the thymus in cases of exophthalmic goiter. More recent studies by

78. Timme, W.: Northwest Med. **12**:337, 1923.

79. Emerson, H.: Status Lymphaticus in Adults: Its Clinical Diagnosis and Importance, Arch. Int. Med. **13**:169 (Jan.) 1914.

80. Kundrat, R. v.: Wien. klin. Wchnschr. **6**:505, 1893.

Hektoen,[81] Capelle,[82] Matti,[83] Gierke,[84] Giordano [85] and others indicate that thymic enlargement is present in practically all cases of primary exophthalmic goiter. Marie [86] first pointed out the probable regeneration of the thymus in cases of exophthalmic goiter, and one must now assume that this occurs in most of the adults who devolop the disease. The regional lymph glands and spleen are also usually enlarged. The anatomic conditions, therefore, are often identical with those of status lymphaticus. Many patients have died under circumstances closely resembling the sudden death in status lymphaticus. Some writers assume that these are cases of exophthalmic goiter complicated by status lymphaticus. Generalized lymphoid hyperplasia and hypersusceptibility are too constantly associated with exophthalmic goiter for this kind of explanation. It is more probable that the two diseases have some basic factor in common.

Prominence of the lymphoid tissues and thymus is also frequently observed in Addison's disease and in chlorosis. Since sufficient injury of the suprarenal glands will cause regeneration of the thymus, it is evident that a close relation must exist between status lymphaticus, exophthalmic goiter, Addison's disease and chlorosis, both etiologically and pathologically. Enlargement of the thymus is also found in persons with simple goiter—especially endemic congenital goiter, in certain goitrous cretins and regularly in persons with acromegaly and with anencephaly.

The close association of rickets and status lymphaticus as regards their morbid anatomy has been referred to. The nature of this association may become clearer when measures for the prevention of rickets shall have been carried out over a longer period.

Ohlmacher has emphasized the association of idiopathic epilepsy and status lymphaticus as a result of the frequent occurrence of prominent lymphoid tissues and thymus in fatal cases. Finally, there is some evidence that asthma, hay-fever and eczema, at least in children, are related to status lymphaticus.

LOWERED RESISTANCE

The close relationship between status lymphaticus and lowered resistance or increased susceptibility is the most outstanding known clinical manifestation both of status lymphaticus in man and experimental status lymphaticus in animals. The lowering of resistance is not specific, but

81. Hektoen, L.: Internal. M. Mag., Phila. **4**:584, 1895-1896.
82. Capelle, W.: Deutsche med. Wchnschr. **37**:1771, 1911.
83. Matti, H.: Deutsche Ztschr. f. Chir. **116**:427, 1912.
84. Gierke, E.: München. med. Wchnschr. **54**:761, 1907.
85. Giordano, A. S.: J. Indiana M. A. **16**:362, 1923.
86. Marie, P.: Bull. et mém. Soc. med. d. Hôp. de Paris **10**:136, 1893.

it can be demonstrated with a great variety of physical and chemical agents. Drugs occupy the most prominent place as a cause of death of persons with status lymphaticus. Indeed, one can determine approximately the date of the introduction of some of the most important drugs and therapeutic agents by looking up reports of cases of status lymphaticus in the literature, as, for example, the introduction of chloroform, ether, cocaine, antitoxins and antiserums, vaccines, arsphenamine and many other drugs.

Anesthetics.—Of all the drugs, anesthetics perhaps are most frequently mentioned in the literature, chloroform heading the list (Kundrat[87]). All general anesthetics are dangerous, as shown by Blake.[88] Exophthalmic goiter, Addison's disease and chlorosis belong in the same class with status lymphaticus, not only as regards their pathologic anatomy, but also as regards the dangers of anesthetics and other drugs, another of the many indications of a close biologic relationship between these diseases.

Although literature regarding animals is not available, while working in Cleveland, I was struck by the frequency with which young dogs with goiter died under ether anesthesia. The technician who had for many years assisted in the preparation of class work in physiology told me that he also was aware of this danger, and that he particularly avoided using dogs with goiter or allowing students to use them, because they were so frequently killed during the attempt to anesthetize them with ether. Also, while it is not referred to in the literature, I have several times seen morphologically typical cases of status lymphaticus in dogs and cats that have died suddenly from what appeared to be trivial causes. In several dogs I have seen goiter associated with large lymphoid tonsils, hypertrophy of the lymphoid tissue at the base of the tongue and in the pharynx, large cellular thymus, enlarged spleen and prominent mesenteric and intestinal lymphoid tissue. In cats the lymphoid tissues are normally so prominent that only cases in which extreme lymphoid hyperplasia is associated with focal necrosis is the condition designated as status lymphaticus.

The subcutaneous administration of serum has been followed by sudden death. One of the earliest and most discussed instances was the death of Professor Langerhans' son following the injection of diphtheria antitoxin. The administration of vaccines has been followed by death in persons with general lymphoid hyperplasia. In such cases the question arises whether death is due to the physical and psychic shock of introducing the needle or to the action of the drug. Shock must play a rôle in cases in which persons die immediately after the needle puncture just as it plays a rôle in cases in

87. Kundrat, R. v.: Wien. klin. Wchnschr. **8**:1, 26, 44 and 64, 1895.

88. Blake, J. A.: Ann. Surg. **35**:745, 1902.

which death occurs as soon as the person enters the water, although postmortem examination, as pointed out by Paltauf and Nordmann,[89] does not indicate drowning. So also an abnormal susceptibility to shock must explain deaths following trivial surgical and medical procedures, such as extraction of teeth, removal of adenoids and tonsils and venous puncture, and accidents, such as fracture of bones; such deaths are difficult to explain without assuming a deleterious hypersusceptibility to psychical and physical shock. However, psychic and physical shock alone is a relatively unimportant cause of death following the administration of drugs; in most cases, the cause is hypersusceptibility to the drug or poison. Some observers have suggested that in cases of status lymphaticus death is due to anaphylaxis; but anphylaxis would account for only a small portion of these fatalities since death occurs after the injection of nonprotein material as well. The cause of death is more mysterious and deep-seated. Wiesel's view that it is due to the injurious raising of the vagus tone in association with insufficiency of the chromaffin and sympathetic nervous system, while vague and indefinite, certainty touches on one of the vital factors involved.

Infectious Diseases.—There is surprisingly little literature on the question of hypersusceptibility to infection in cases of status lymphaticus, and undoubtedly this condition does not figure as prominently in the conception of the factors which determine the prognosis in acute infections as it deserves. The oldest relation to infection is the association of scrofula and tuberculosis of the bone with the lymphatic constitution. Virchow was impressed with the fulminant course of cholera in lymphatic individuals. Ortner[90] referred to it in relation to pneumonia, and Virchow, Heller and many others, in relation to typhoid fever. Daut[91] has demonstrated in Escherich's clinic that diphtheria tends to assume a particularly malignant form in infants and in children with the lympathic constitution. Thus, twenty-three of seventy-nine persons who died from diphtheria in Graz showed anatomic manifestations of status lymphaticus. Daut pointed out that susceptibility to diphtheria in cases of status lymphaticus shows itself in several ways. For example, in an otherwise mild epidemic, these children died early of apparently overwhelming intoxication in which the anatomic lesions of diphtheria seemed too slight to explain the sudden death. Fatal termination resulted despite the prompt and free use of antitoxin.

Blumer[92] reported two cases, one of tetanus and one of streptococcic infection, which were unusually acute. Brigidi and Piccoli[93] referred to

89. Nordmann, A.: Cor. Bl. f. schweiz. Aerzte **19**:202, 1889.
90. Ortner, N.: Wien. klin. Wchnschr. **4**:2 and 27, 1891.
91. Daut, M.: Jahrb. f. Kinderh. **47**:141, 1898.
92. Blumer, G.: Bull. Johns Hopkins Hosp. **14**:270, 1903.
93. Brigidi, V., and Piccoli, E.: Beitr. z. path. Anat. u. z. allg. Pathol. **16**: 388, 1894.

cases of typhoid fever with rapidly fatal courses. McNeil and McGowan, also Duncan,[94] have reported a series of cases resembling pneumonia in boys' industrial schools in which the rapidly fatal course was out of proportion to the apparent severity of the disease; he suggested that status lymphaticus might be an underlying factor. Elser,[95] in reporting an epidemic of cerebrospinal meningitis, pointed out that it was highly significant that all six of the cases of fulminant meningitis had the anatomic features of status lymphaticus, while those cases in which death occurred more than seventy-two hours after the onset of symptoms did not show this picture. He added that there could be no doubt that status lymphaticus is an important factor in determining the rapidly fatal course of meningitis. Symmers also emphasized the susceptibility of persons with status lymphaticus to infections, and the rapidly fatal course of such diseases as acute infectious endocarditis, meningitis and typhoid fever in these patients.

Bircher[96] (1922) reported that in 276 cases of tetanus, diphtheria, appendicitis and acute cholecystitis, status lymphaticus was present in 80 per cent of the thirty-five persons who died.

Experimental Studies.—Lewis[97] first showed that suprarenalectomy lowered the resistance of rats to morphine as much as 400 times. This was confirmed by Scott,[98] and further work by Lewis,[99] Scott, Také and Marine, Jaffe and Marmorston has confirmed and added to the fact that suprarenalectomy causes the greatest lowering of resistance or increase in susceptibility of any known experimental procedure. When this knowledge is added to the fact that suprarenalectomy causes a rapid regeneration of the thymus and lymphoid tissues—a true experimental status lymphaticus—in rabbits and in rats, the conclusion that a deficiency of some suprarenal and gonadal function is a major factor in the etiology of status lymphaticus and in the lowered resistance seen both in the spontaneous and in the experimentally produced lymphatic state appears justified. As shown by Také and Marine and and by Jaffe and Marine, suprarenalectomized rabbits and rats may fully retain their capacity to form antibodies (hemolysin, agglutinin), although their resistance is greatly reduced. This apparent paradox has some confirmation in Tanabe's study on the effects of typhoid vaccine in cases of status lymphaticus occurring in the Japanese army. He found that while alarming reactions sometimes occurred when the ordinary dose of vaccine was administered, the capacity to produce agglutinin was not impaired.

94. Duncan, K. M.: Brit. M. J. **1**:1317, 1913.
95. Elser, W. J.: J. M. Research **14**:89, 1905.
96. Bircher, E.: Deutsche Ztschr. f. Chir. **176**:362, 1922.
97. Lewis, J. T.: Rev. Asoc. méd. argent. **33**:629, 1920.
98. Scott, W. J. M.: J. Exper. Med. **38**:543, 1923.
99. Lewis, J. T.: Am. J. Physiol. **64**:503, 1923.

CLINICAL DIAGNOSIS OF STATUS LYMPHATICUS

The discovery of constant and characteristic symptoms and signs which the clinician can recognize on routine examination is the greatest practical need in connection with this syndrome. Such criteria would warn the physician of the liability to sudden death from slight causes which is the special danger associated with this physiologic defect.

The search for such diagnostic criteria is beset with great difficulties. The first and foremost difficulty, perhaps, is that normally the lymphoid tissues are prominent in infants and in children; second, that all degrees of status lymphaticus exist, so that no sharp division is possible between normal and abnormal even after the age of puberty; third, that spontaneous recovery tends to occur as age advances, and fourth, that the syndrome may be acquired, as shown by the fact that it is readily reproduced experimentally in certain animals (rabbit, rat).

Many authors have searched for and attempted to define diagnostic criteria of clinical importance, notably Escherich,[100] von Neusser [101] and, in this country, Norris,[102] Emerson and Symmers. The usual signs of a pale, thin, velvety skin, enlarged tonsils, superficial lymph glands and thymus and lymphocytosis are not constant occurrences. Schridde is of the opinion that enlargement of the lymphoid follicles at the base of the tongue is a constant symptom in cases of status lymphaticus, though present in other conditions, especially in nervous and mental diseases of youth. When the lingual follicles are enlarged, Schridde believes that careful search should be made for other signs. In view of the present conception of the physiologic defect underlying status lymphaticus, it is not likely that tissues with so great a capacity for rapid hyperplasia and for equally rapid involution as the thymus and lymph glands would show morphologic evidence of specific diagnostic importance in this constitutional anomaly. This is illustrated in the controversy among pathologists as to whether an anatomic diagnosis of status lymphaticus in infants is justifiable.

Some tests of resistance or susceptibility that could be applied clinically would seem more logical and of greater practical value, since hypersusceptibility is the most characteristic physiologic manifestation of status lymphaticus. It is also the most characteristic reaction so far found in experimentally produced status lymphaticus in rabbits and in rats. The systemic, or possibly the dermal, reaction to some drug or toxin should be sought for in the hope of finding one that, given in minimum doses without danger, would produce a characteristic reaction.

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100. Escherich, K.: Berl. klin. Wchnschr. **33**:645, 1896.

101. Von Neusser, E.: Ausgewöhlte Kapitel der klinischen. Symtomatologie u. Diagnostik, Vienna and Leipzig, 1911, part 4, p. 197.

102. Norris, C., quoted by Symmers (footnote 67).

Epinephrine as used in the Goetsch test and insulin are examples of drugs that might be used. Insulin has the advantage that untoward effects could be controlled, although any test involving hyperdermic injection is dangerous.

CAUSE OF DEATH IN STATUS LYMPHATICUS

A vigorous controversy has existed for the past 100 years regarding the cause of death. The following theories have been expounded: 1. Death is due to pressure of an enlarged thymus on the trachea, blood vessels and nerve trunks. 2. It is a result of the constitutional defect manifesting itself through an injurious raising of the vagus tone, together with a deficiency of the chromaffin system and weakness of the sympathetic system. 3. It is a result of hypersusceptibility to physical and chemical agents. 4. It occurs through anaphylaxis. 5. It results from an abnormal thymus secretion of a general lymphotoxemia.

As long as hypertrophy of the thymus was looked on as the chief lesion in status lymphaticus, it was inevitable that pressure should be considered as a major factor in the cause of death, especially in persons under 1 year of age. This view was first vigorously opposed by Friedleben, who failed to find evidence of pressure, and in some cases not even enlargement of the thymus. Paltauf also opposed the view on the basis that the thymic changes were only symptomatic; he said that while pressure effects occasionally occur, these are incidental. Elaborate studies have been made by Schoeppler [103] and others in the attempt to show the amount of pressure necessary to compress the trachea and the conditions under which sufficient pressure could be exerted, as for example, following sudden congestion of the thymus with the head pulled back.

There is no question, however, that occasionally tracheostenosis may be produced by an enlarged thymus. Jackson [104] and others have demonstrated this during life by bronchoscopic examination. Siegel, Koenig, Perrucker and others have reported cures by partial removal or by anchoring the thymus. The anatomic studies of Noback [105] indicate that compression of the innominate artery and vein, trachea and recurrent laryngeal nerves by the thymus could occur in the late fetal days and in the early days of postnatal life.

In infants up to 1 year of age, the diagnosis of thymic stridor has come to be applied to almost all cases of respiratory stridor. If roentgen-ray examination appears to confirm the existence of a large thymus, the evidence in favor of thymic origin is usually assumed to be complete.

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103. Schoeppler, H.: Centralbl. f. allg. Pathol. u. path. Anat. **25**:289, 1914.

104. Jackson, C.: Thymic Tracheostenosis, Tracheoscopy, Thymectomy, Cure, J. A. M. A. **48**:1753 (May 25) 1907.

105. Noback, G. J.: Contributions to Topographic Anatomy of Thymus Gland, Am. J. Dis. Child. **22**:120 (Aug.) 1921.

The relief which roentgen-ray treatment gives, as first reported by Friedlander, and explained as due to the destructive effects of the roentgen ray on the thymus is not proof of a thymic origin, because (1) the relief is occasionally too rapid, and (2) the benefit may be due to other and more distant effects of the roentgen ray. The most important evidence against a thymic stridor or asthma is that it may be present when the thymus is small or absent when the thymus is large. Pathologists have rarely reported evidence of tracheal compression, even though it has been looked for constantly (Boyd [106]). Many pediatricians (Finkelstein, Abt and Helmholtz) are skeptical of the clinical existence of a thymic asthma. Von Sury,[107] Pappenheimer and Wasson [108] have pointed out that bronchial, pharyngeal and sinus infections, mucus and many other factors may produce a stridor in infants which has nothing to do with the thymus or status lymphaticus.

One must conclude, therefore, that in the great majority of cases no clinical or postmortem evidence exists that death is caused by compression, and that the explanation of thymic asthma or thymic death is not so simple, or at least that pressure effects are inadequate in the absence of a constitutional predisposition to account for death.

The symptoms of a fatal attack of so-called thymic asthma are characteristic and have been so clearly described by Pott [109] that his description is quoted herewith:

> The child unexpectedly and suddenly throws back its head, makes noisy gasping efforts at respiration and rolls its eyes upward. The pupils dilate, while the face and tongue become cyanotic and swollen. The veins of the neck stand out. The hands are clenched with the thumbs in the palms. The forearms are strongly pronated and adducted. The lower extremities are extended with the great toes adducted and dorsally flexed. The back is arched. Slight twitching movements of the facial muscles occur and a few unavailing efforts at respiration are made. The convulsion stops and the muscle relaxation of death occurs. The cyanosis lessens, the face becomes ashy and the patient is dead. The heart action had ceased at the beginning of the attack.

The immediate cause of death is stoppage of the heart, as pointed out by Pott, Escherich, Griffith [110] and many others. These observers assume the existence of a neurosis of some sort, in which hyperexcitability of the vagus coupled with a weakness of the sympathetic system—an autonomic imbalance—is present, and is the basis of the cardiac stoppage.

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106. Boyd, E.: Growth of the Thymus; Its Relation to Status Thymicolymphaticus and Thymic Symptoms, Am. J. Dis. Child. **33**:86 (June) 1927.
107. Sury, K. von: Vrtljschr. f. gerichtl. Med. **36**:88, 1908.
108. Wasson, W. W.: Thymic Stridor, J. A. M. A. **89**:1025 (Sept. 24) 1927.
109. Pott: Jahrb. f. Kinderh. **34**:118, 1892.
110. Griffith, J. P. C.: Am. Med. **5**:989, 1903.

The view that sudden death in cases of status lymphaticus is anaphylactic has been advanced especially by Symmers,[111] who assumes that sensitization and shock are the result of the liberation of nucleoprotein from necrotic germinal centers. That persons with status lymphaticus are more susceptible to shock than normal persons is suggested by the experimental work of Kepinow [112] and Flashman,[113] who found that partially suprarenalectomized guinea-pigs and rats are more susceptible to anaphylaxis than normal animals. It does not appear, however, that anaphylaxis is of greater importance than many other factors which lead to sudden death, but rather that it is an additional means of demonstrating lowered resistance.

The view that deaths in cases of status lymphaticus are due to a thymus or to lymphotoxemia originated in Svehla's observation that thymus extracts lowered blood pressure and accelerated the heart rate—manifestations that are now known to be produced by many foreign proteins. On the basis of these observations, he suggested that death caused by the thymus was due to hyperthymization, and Escherich thought that the lowered resistance to infectious diseases might be thus explained. This hypothesis has only the relatively constant pathologic condition of lymphoid and thymus hyperplasia in its support.

The observations of MacLean and Sullivan,[114] who found the blood sugar markedly lowered in three cases of status lymphaticus in infants and associated with insulin-like convulsions, offer a promising lead. They interpret their results as further support of the hypothesis of suprarenal insufficiency as the cause of status lymphaticus, i.e., a lack of the antagonistic action of epinephrine. Hypoglycemia has also been noted in other conditions closely related to status lymphaticus; for example, in exophthalmic goiter and in Addison's disease and following experimental suprarenalectomy in animals.

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111. Symmers, D.: Status Lymphaticus, Am. J. Dis. Child. **14**:463 (Dec.) 1917.

112. Kepinow, L.: Compt. rend. Soc. de biol. **87**:327, 1922.

113. Flashman, D. H.: J. Infec. Dis. **38**:461, 1926.

114. MacLean, A. B., and Sullivan, R. C.: Am. J. M. Sc. **171**:659, 1926.

Notes and News

Death of Johannes Fibiger.—Johannes Fibiger, professor of pathologic anatomy in the University of Copenhagen, who recently was awarded a Nobel prize in medicine for his work on carcinoma of the stomach in rats following infestation with *Spiroptera neoplastica*, died on January 31, at the age of 61 years.

Material for the Study of Comparative Anatomy, Normal and Pathologic.—The laboratory of the Philadelphia Zoological Society, Herbert Fox, director, will provide such material as may be spared to accredited workers on comparative anatomy, normal and pathologic.

Philadelphia Pathologic Society.—J. H. Austin has been elected president of the Philadelphia Pathological Society; T. Grier Miller, vice-president; B. Lucke, secretary-treasurer, and Frank W. Konzelman, recorder.

Undulant Fever.—The Camera Medica of Malta and the Malta branch of the British Medical Association urges the adoption of the name of undulant fever in place of Mediterranean or Malta fever and other geographic names.

Delafield Professorship of Pathology.—The alumni association of the College of Physicians and Surgeons of Columbia University has donated $128,000 to the university to found a professorship in pathology. The money will be held in trust until $200,000 is accumulated. The professorship will be named after Francis Delafield (1841-1915), professor of pathology and the first director of the pathologic laboratory of the College of Physicians and Surgeons. This laboratory was founded by the alumini association in 1877.

Death of James Todd.—James Campbell Todd, professor of pathology in the University of Colorado School of Medicine from 1911 to 1916, professor of clinical pathology since 1916, and joint author with A. H. Sanford of "Clinical Diagnosis by Laboratory Methods," died on Jan. 6, 1928, at the age of 54 years.

Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation.—During 1927, the foundation made twenty-four grants, seventeen of which were to scientists in countries outside the United States. Fifty-five applications were received. In the four years that the foundation has existed, fifty-five grants have been made. At present "researches are favored that are directed toward the solution of problems in medicine and surgery or in branches of science leaning on medicine and surgery." Applications for grants for 1928-1929 should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Boston 14, Mass., before May 15, 1928.

Illness of Alice C. Evans.—Alice C. Evans, bacteriologist at the Hygienic Laboratory in Washington and recently elected president of the Society of American Bacteriologists, is a victim of a laboratory infection with undulant fever.

Abstracts from Current Literature

Pathologic Physiology

A Comparison in Normal, Thyroidectomized and Hypophysectomized Rats of the Effects Upon Metabolism and Growth Resulting from Daily Injections of Small Amounts of Thyroid Extract. Philip E. Smith, C. F. Greenwood and G. L. Foster, Am. J. Path. **3**:669, 1927.

Small doses of fresh extracts in salt solution of sheep thyroids caused pronounced growth and increase in the suprarenals in thyroidectomized rats, but did not have any effect in rats subjected to removal of the hypophysis.

Concerning the Effect of Diet on the Concentration of the Nonprotein Sulphur of Blood. W. Denis and L. Reed, Am. J. Physiol. **83**:47, 1927.

In dogs fed successively on diets low and high in sulphur and nitrogen compounds, no relationship could be observed between the concentrations of nonprotein sulphur of the blood and the rate of excretion, or the concentration of these substances in the urine, nor to the content of sulphur or nitrogen in the food. The level of the inorganic blood sulphates was closely associated with volume of urinary secretion, but otherwise there was no demonstrable relationship.

H. E. Eggers.

Blood Regeneration in Severe Anemia, X. G. H. Whipple and F. S. Robscheit-Robbins, Am. J. Physiol. **83**:60, 1927.

Healthy dogs in a condition of severe secondary anemia can conserve (dog) blood hemoglobin introduced intraperitoneally or intravenously to a remarkable degree, as much as from 80 to 90 per cent of this hemoglobin appearing in the form of new red cells. When red cells are fed, only from 5 to 20 per cent utilization was observed. There was 40 per cent utilization with a pancreatic digest of the red cells of dogs introduced intravenously. Muscle hemoglobin given intravenously was not well tolerated and had a low renal threshold. There appeared to be some evidence of its utilization in the formation of new red cell hemoglobin. No convincing evidence of "pigment circulation" or of the utilization of bile pigment in the formation of red cell hemoglobin was found.

H. E. Eggers.

Blood Regeneration in Severe Anemia, XI. F. S. Robscheit-Robbins and G. H. Whipple, Am. J. Physiol. **83**:76, 1927.

Small amounts of iron salts (citrate, chloride) added to the diet of dogs rendered anemic by bleeding affected the production of the hemoglobin variably, causing an increase at times, at times not. This, the writers infer, may be due to the variable presence of an actual iron deficiency, or to salt unbalance. When to the iron feeding is added feeding with liver or kidney, an effect is obtained equal to the sum of the expected reactions, so that the effect of the organ feeding does not appear to be due to its iron content.

H. E. Eggers.

Blood Pressure Following Adrenalectomy. J. M. Rogoff and R. Dominguez, Am. J. Physiol. **83**:84, 1927.

Blood pressure determinations made on suprarenalectomized dogs daily for periods of from twelve to thirty-seven days did not show any conspicuous

change during the period of good health. With the onset of terminal symptoms a few days before death there was a decided and progressive fall of pressure.

H. E. Eggers.

The Respiratory Quotient of Resting Muscle. H. E. Himwich and W. B. Castle, Am. J. Physiol. **83**:92, 1927.

The respiratory quotient of the muscle of a dog was studied by analysis of the oxygen carbon dioxide content and capacity of arterial and venous blood, in trained dogs, decerebrate dogs and decerebrate dogs with isolated muscle circulation. While wide individual variations were obtained, the averages of the respiratory quotients obtained from the blood and from the expired air were closely similar, and on the basis of these averages it was found that resting muscle in situ has a quotient not of unity, but close to that of the whole body. Apparently in normal conditions it oxidizes not only carbohydrate, but fat or protein or both as well, in much the same proportions as the rest of the body.

H. E. Eggers.

Studies on Diabetes Insipidus: The Diuretic Substance. H. Bourquin, Am. J. Physiol. **83**:125, 1927.

From the mamillary bodies of the brains of dogs there was extracted a substance having diuretic properties; this was present in much larger quantities in material obtained from animals suffering from experimental diabetes inspidus, and was not found in extracts of other portions of the brain. It was not precipitated by phosphotungstic acid. A similar substance, in that it had diuretic properties of the same physiologic character and was not precipitated by phosphotungstic acid, was demonstrated in the blood of dogs with experimental diabetes insipidus, but not in that of normal dogs. This substance was less active after charring, was relatively stable in neutral solutions and when dried, and was destroyed by long boiling in a weakly alkaline solution. This substance could not be demonstrated to be present in the urine.

H. E. Eggers.

Further Studies on the Alleged Interrelationship of the Pancreas and the Thyroid. L. B. Shpiner, Am. J. Physiol. **83**:134, 1927.

The hyperglycemia and glycosuria which follow thyroid medication appear to be due largely to the increased basal metabolic rate. The injection of sodium nucleinate, which is followed by an increased basal metabolic rate with fever, produces a similar hyperglycemia, so that apparently the relationship between thyroid and pancreas is only an indirect one.

H. E. Eggers.

Insulin Anhydremia. D. L. Drabkin and H. Shilkret, Am. J. Physiol. **83**:141, 1927.

The reaction to insulin was influenced markedly by the water reserve of the dogs studied. In dogs that had been water-starved for several days, large doses of insulin caused a more profound anhydremia than in normal animals. Spastic convulsions occurred in the latter only, but whereas these invariably recovered when given glucose, the dogs that had been deprived of water succumbed.

H. E. Eggers.

ABSORPTION OF INSULIN FROM THE ALIMENTARY TRACT OF DEPANCREATIZED DOGS, WHEN PROTECTED BY BLOOD SERUM. J. R. MURLIN and E. E. HAWLEY, Am. J. Physiol. **83**:147, 1927.

To a series of depancreatized dogs insulin suspended in blood serum was administered by stomach tube; observations on these dogs leave little doubt that administration by this method is effective. In some instances the respiratory quotient was raised as effectively as following subcutaneous injection, and several times the urine became completely sugar-free even with animals on full diet. The effect on blood sugar is less sudden and pronounced than when the subcutaneous route is used, hypoglycemic shock never having been observed after the feeding of insulin. This the writers ascribe to the protective action of the liver.

H. E. EGGERS.

REGULATION OF CIRCULATION; RELATIVE IMPORTANCE OF NERVOUS, ENDOCRINE, AND VASCULAR REGULATION IN THE RESPONSE OF THE CARDIAC OUTPUT TO ANOXEMIA. T. R. HARRISON, A. BLALOCK, C. PILCHER and C. P. WILSON, Am. J. Physiol. **83**:284, 1927.

On the basis of experiments on morphinized or trained dogs, the writers conclude that in the functional control of circulatory minute volume chemical regulation is of greater importance than that of the nerves. The cardiac nerves which influence cardiac rate do not play a rôle in this regulation of output. The chemical regulation is of at least two types — by hormones, chiefly of suprarenal origin—and by the blood gases. Of these, the oxygen tension in the heart muscle appears to be the most important element.

H. E. EGGERS.

EFFECT OF EXPERIMENTAL PYLORIC STENOSIS ON GASTRIC SECRETION. A. C. IVY, E. H. DROEGEMUELLER and J. L. MEYER, Arch. Int. Med. **40**:434, 1927.

Experimental pyloric obstruction was made in twelve dogs with a Pawlow pouch. Seven of the dogs survived for a period of from three and one-half to seven and one-half months. The stenosis first caused a decrease in gastric secretions; later, four of the seven dogs showed hypernormal secretion, one a normal secretion and two a decreased gastric secretion. The indirect observation of Hamburger and Friedman is confirmed, namely, that experimental pyloric obstruction causes a hypernormal secretion of gastric juice in some cases. The point is emphasized that before Pawlow pouches are used it should be shown that they reflect the secretory activity of the stomach. A marked hypertrophy of the stomach occurred in four of the seven dogs.

AUTHORS' SUMMARY.

DISEASES OF THE LIVER. A. M. SNELL, C. H. GREENE and L. G. ROWNTREE, Arch. Int. Med. **40**:471, 1927.

The bilirubin content of the serum tends to decrease spontaneously in the later stages of obstructive jaundice, presumably owing to a decrease in the production of pigment. With the development of cirrhotic changes in the liver the excretion of bilirubin apparently becomes increasingly difficult, and in two dogs cholecystenterostomy with temporary relief of the biliary obstruction did not significantly affect the level of bilirubin. The changes in the bromsulphalein test were in entire agreement with those previously obtained with phenoltetrachlorphthalein. The retention of dye in its development closely paralleled the degree of retention of bile. Once retention was established, the bromsulphalein

readings were relatively constant and its retention more persistent than that of either the bile acids or the bilirubin. The intensity of the Pettenkofer reaction given by the blood increased rapidly after obstruction. The rate of accumulation of bile acids under these circumstances was determined by the activity of the gallbladder, as in the case of the bilirubin. Later the readings tended to decrease, and returned approximately to the normal value, indicating probable failure of the synthesis of the bile acids. The changes in the blood corresponded with the reported changes in the urinary excretion of the bile acids. The authors believe, therefore, that the changes in the Pettenkofer readings may be considered indicative of changes in the bile acid content of the blood. Intravenously injected bile acids are rapidly removed from the blood stream of normal animals. This elimination was interfered with by an obstructive jaundice, and injected bile acids were retained in the blood stream, the degree of retention paralleling the changes in the other tests. These experimental data are a counterpart of, and in agreement with, the changes observed clinically in obstructive jaundice and in biliary cirrhosis secondary to obstruction of the bile passages.

AUTHORS' SUMMARY.

THE SPLANCHNOPERIPHERAL BALANCE DURING CHILL AND FEVER. WILLIAM F. PETERSEN and ERNST F. MÜLLER, Arch. Int. Med. **40**:575, 1927.

The production of bacterial chill and fever is the result of the fixation of the splanchnoperipheral autonomic balance. The entrance of bacteria into the blood stream is followed by their fixation by the reticulo-endothelial elements of the splanchnic area. This (depending on the toxicity of the organisms) is followed by a marked stimulation of these cells and of the organs in which they occur —liver, spleen, bone-marrow and gastro-intestinal system. This stimulation involves a parasympathetic status of the organ group and with it a sympathetic orientation of the peripheral organs. In this peripheral group, the muscles are oriented in the same direction as the skin and vascular tissues. The intense sympathetic orientation, which arrests the activity and restricts the blood supply, is an adaptation to the fundamental alterations in the condition of existence of the whole organism. The muscle tremor itself is the expression of the intense sympathetic orientation, augmented to such a degree that it cannot be overcome by will, as is still possible in the chill accompanying the external application of cold. The tremor itself, presumably a clonic effect in muscle with increased tonus, may be associated with the local effect of metabolic products accumulated when vascular constriction takes place, rather than a phenomenon due to the mere deprivation of oxygen. The tremor is not associated with increased production of heat and is to be regarded as a phenomenon analogous to that studied in smooth muscle during so-called "muscle blockade."

AUTHORS' SUMMARY.

SUPRARENAL CARCINOMA WITH PUBERTAS PRAECOX IN YOUNG BOY. M. B. GORDON and E. J. BROWDER, Endocrinology **11**:265, 1927.

Gordon and Browder report the case of a boy, aged 3 years, who presented symptoms of pubertas praecox, the onset being noticed at the age of 9 months. He was of herculean build, had a mannish voice, acne, pubic hair, light mustache, external genitalia of a boy, aged 16 years, and premature ossification. His mentality was somewhat below that of a child of his actual age. Autopsy showed a carcinoma of the left suprarenal gland which extended into the left suprarenal vein and inferior vena cava with metastases in the lungs. The right suprarenal gland and right suprarenal vein were absent. That portion

of the left suprarenal gland not involved by the tumor showed a picture generally found at the time of puberty; the thymus showed involution; the thyroid contained colloid; the pancreas, pituitary and pineal glands were normal. The testes were immature and did not show any spermatogenesis.

THE NORMAL PIGMENT OF THE URINE: I. THE RELATIONSHIP OF URINARY PIGMENT OUTPUT TO DIET AND METABOLISM. D. L. DRABKIN, J. Biol. Chem. **75**:443, 1927.

II. THE RELATIONSHIP OF THE BASAL METABOLISM TO THE OUTPUT OF THE NORMAL URINARY PIGMENT. Ibid. **75**:481, 1927.

The normal urinary pigment is an endogenous product and is eliminated at a rate which may be proportional to the intensity of the endogenous metabolism. The output of pigment is increased by stimulation of the metabolism, by fasting and by administration of acids. It is decreased by administration of alkalis and by removal of the thyroid glands (in dogs), and is extraordinarily high in persons with exophthalmic goiter. A comparison of the pigment excretion of rats, dogs and men of varying sizes indicates a constancy in the quantity of urinary pigment excreted per hour per unit of surface area.

ARTHUR LOCKE.

ZINC AND NORMAL NUTRITION. R. B. HUBBELL and L. B. MENDEL, J. Biol. Chem. **75**:567, 1927.

Zinc is generally distributed in foods of both plant and animal origin. It is not stored by mice to an appreciable extent. A slight growth stimulating effect, more manifest with the females than the males, was obtained by slightly increasing the zinc content of a diet low in zinc.

ARTHUR LOCKE.

SOME EFFECTS OF SYNTHALIN ON METABOLISM. N. R. BLATHERWICK, M. SAHYUN and E. HILL, J. Biol. Chem. **75**:671, 1927.

Synthalin is a guanidine derivative which has been reported to have an insulin-like action on the normal and diabetic organism. Hypoglycemic action does not follow intragastric administration of the drug to rabbits. Parenteral administration produces an acute nephritis, with accompanying injury to the liver.

ARTHUR LOCKE.

CHANGES IN THE OXYGEN CAPACITY OF THE BLOOD PIGMENT OF RABBITS FOLLOWING THE ADMINISTRATION OF NITROBENZENE. B. B. STIMSON, J. Biol. Chem. **75**:741, 1927.

The intragastric administration of nitrobenzene to rabbits causes the formation of a hemoglobin derivative which is incapable of carrying oxygen but which is reduced by hyposulphite to active hemoglobin. The rate and amount of its formation appear to be increased following splenectomy. The new derivative is not identical with methemoglobin.

ARTHUR LOCKE.

THE INFLUENCE OF PROTEIN-FREE LIVER AND SPLEEN EXTRACTS ON THE BLOOD REGENERATION AND RESPIRATORY EXCHANGE OF ANEMIC RABBITS. A. JENEY, J. Exper. Med. **46**:689, 1927.

Respiratory exchange measurements may be used for gaining further evidence concerning the body changes during anemia, and are complementary to the hematologic and histologic data. The heat production during anemia was

slightly decreased. At the third week it began to rise. A protein-free liver extract has accelerated blood regeneration and at the same time increased the respiratory exchange of anemic animals. A protein-free spleen extract has distinctly lowered the respiratory exchange of normal animals. The metabolism of anemic animals thus treated was practically the same as before bleeding and treatment. The recovery of the animals treated with spleen extract was not complete during the period of observation. This extract may have been somewhat toxic. In spite of this disturbing factor we are not inclined to accept the view of C. D. and E. W. Leake and Thalhimer that the spleen takes part in the stimulating effect on blood regeneration when given in combination with red bone marrow by mouth.

AUTHOR'S SUMMARY.

DEFICIENCY IN VITAMIN A AND METAPLASIA. HARRY GOLDBLATT and MARIA BENISCHEK, J. Exper. Med. **46**:699, 1927.

A dietary deficiency of vitamin A alone is adequate to induce metaplasia of columnar, cuboidal and transitional epithelia to the squamous, keratinizing type in some organs. Epithelial metaplasia of the squamous keratinizing type is of such frequency in young rats kept on a diet deficient in vitamin A for a long period of time (ten weeks or longer) as to constitute a good morphologic indicator of the deficiency of this vitamin in the diet. The metaplastic changes are as frequent and as great in rats on a diet deficient in vitamin A alone as in those on a diet deficient in vitamins A and D. Inadequate food, provided the vitamins are supplied, does not induce the metaplasia.

AUTHORS' SUMMARY.

THE OXYGEN CONTENT OF THE VENOUS BLOOD OF THE DOG AFTER UPPER GASTRO-INTESTINAL TRACT OBSTRUCTION. RUSSELL L. HADEN and THOMAS G. ORR, J. Exper. Med. **46**:709, 1927.

There is a rapid fall in the oxygen content of the venous blood of the dog after obstruction of the upper gastro-intestinal tract. This increased deoxidation is probably due to a combination of several factors. There is much evidence to suggest that active reducing bodies are present in the blood.

AUTHORS' SUMMARY.

AN EXPERIMENTAL STUDY OF DIATHERMY: IV. EVIDENCE FOR THE PENETRATION OF HIGH FREQUENCY CURRENTS THROUGH THE LIVING BODY. RONALD V. CHRISTIE and CARL A. L. BINGER, J. Exper. Med. **46**:715, 1927.

Heating occurs from without inward; deep heating during diathermy is greater than that which results from the application of local heat to the skin; the lung can be heated by diathermy in spite of simultaneous cooling of the wall of the chest. The authors regard these experiments as satisfactory evidence of the passage of the current through the interior of the body.

STUDIES ON NEPHRITIS. PHYSIOLOGIC AND ANATOMIC CHANGES FOLLOWING TEMPORARY ISCHEMIA OF THE KIDNEYS. E. T. MCENERY, J. MEYER and A. C. IVY, J. Lab. & Clin. Med. **12**:349, 1927.

Ischemia of the kidney for periods of from thirty to sixty minutes in the dog causes degenerative changes that frequently result in the formation of a "small white kidney." Both kidneys are usually not affected to the same extent, the most probable explanation for the difference being a variability in the

amount of collateral circulation. Dogs may or may not survive a thirty to sixty minute period of ischemia of both kidneys. The majority, however, survive an ischemia of forty-five minutes. The symptoms that result from such a procedure are vomiting, anorexia, asthenia and anuria. Albumin and cells (kidney cells, red and white blood cells) are present in the urine for varying periods. Albumin persists for from one to four months. The blood urea is always increased, and in the cases in which a severe reaction occurs, it may be as high as 0.3 Gm. The authors believe that this method is most satisfactory for the study of the effect of nephritis on gastric secretion, or on other physiologic processes, in which it is necessary to avoid the use of toxins or chemicals, which per se might complicate the result.

S. A. LEVINSON.

STUDIES ON NEPHRITIS. GASTRIC SECRETION IN NEPHRITIS. E. T. MCENERY, J. MEYER and A. C. IVY, J. Lab. & Clin. Med. **12**:362, 1927.

Acute nephritis produced in dogs by occlusion of the renal vessels for forty-five minutes decreases, but does not abolish, the gastric secretory response to a meal and to 1 mg. of histamine. The chronic nephritis that follows such a procedure does not appreciably affect gastric secretion. Urea (from 2 to 10 mg. per hundred cubic centimeters) in small amounts has been found in the gastric secretion of most of the normal dogs studied. The intravenous injection of urea causes an increase in the urea in the gastric juice; and associated with the increase in blood urea in experimental nephritis there is an increase in the urea in the gastric juice. Although the gastric glands in nephritis are probably somewhat depressed, as judged from the continuous secretion, they respond to a lactose-tea meal or to an injection of histamine. The authors found urea in the saliva and bile free gastric juice of patients with nephritis, the urea content of the juice being high usually in those that presented high blood urea content.

S. A. LEVINSON.

THE SUPERIOR CERVICAL SYMPATHETIC GANGLION IN ANGINA PECTORIS: A MICROSCOPIC STUDY. SAM L. CLARK, J. Lab. & Clin. Med. **13**:101, 1927.

Specific changes for angina pectoris have not been demonstrated in the superior cervical sympathetic ganglions.

OVARIAN AND PLACENTAL HORMONES. EDGAR ALLEN and EDWARD A. DOISY, Physiol. Rev. **7**:600, 1927.

There may be several hormones produced by the ovaries and placenta. Partial chemical isolation of at least one substance from these sources has been accomplished. Differentiation has not yet been made in material from ovaries and placenta. Characteristic replacement effects have been demonstrated by injections of this active substance. The essential steps in chemical preparation and the properties of the most highly purified products are reviewed. The reactions induced in ovariectomized animals are: (1) hyperemia and growth in all parts of the reproductive tract and in the mammary glands; (2) secretion by uterine glands and the epithelium of the uterine tubes; (3) typical contraction rhythm of uterine and tubal musculature; (4) congestion, swelling and other external signs of estrus; (5) typical female mating reactions and (6) scanty menstruation (in monkeys) after injections were stopped. These results provide experimental data for the comparison of the essential mechanism of the estrual cycle in lower mammals and the menstrual cycle in primates. They should also advance the therapeutic use of ovarian extracts in the clinical treatment of ovarian disorders.

AUTHORS' SUMMARY.

PROTRACTED TREATMENT OF DIABETES BY INSULIN. MARCEL LABBÉ, Ann. de méd. **22**:121, 1927.

Labbé gives in detail the clinical history of twenty-four patients with diabetes who were treated by him with insulin for a long period of time. He discusses at some length the general results obtained by this method of treatment; the mortality and its causes, the evolution of the disease, the amelioration and also instances in which the disease has been apparently arrested, and finally the mechanism of the noted improvement. He does not accept the idea expressed by Allen, Boyd and Robinson, and some other observers who attribute the improvement to regeneration of the islands of Langerhans, noted at necropsy. In the first place the histologic picture seen in the islands is not characteristic enough to permit one to evaluate their physiologic potentialities; then, Labbé, Laignel-Lavastine and Vitry found similar pictures at postmortem examination of persons who died of grave diabetes during the pre-insulin period. Whatever the mechanism of the action of insulin is, a protracted treatment with this hormone leads, according to Labbé, to an arrest of the disease and in some instances to its possible cure.

B. M. FRIED.

A STUDY OF THE RELATIONSHIP BETWEEN THE SPLEEN AND THE AMOUNT OF BLOOD. JOSEPH BARCROFT, Sang. **1**:97, 1927.

The article by Barcroft begins with a quotation from H. Gray, who in 1854 made the statement that the rôle of the spleen is to regulate the quantity and the quality of the blood. The fact that the quantity of the splenic blood varies greatly in different conditions is, according to Gray, a satisfactory evidence demonstrating this particular rôle of the spleen.

The study by Barcroft is a series of ingenious experiments on cats, dogs, rabbits and rats, the purpose of which is to verify Gray's theory.

In the first place, Barcroft reached the conclusion that the amount of circulating blood and also the amount of hemoglobin in the body are not constant. His researches were then directed toward the spleen with the idea that the organ might possibly retain some blood outside of the general circulation. His conclusions are that the spleen in a living animal is much larger than that seen at postmortem examination. This difference in the splenic size is due to the large quantity of blood contained in the pulp of the organ; and that it is richer in figured elements than that of the general circulation He estimated, moreover, that the spleen of a cat weighing from 2 to 3 Kg. contain about 20 cc. of blood which corresponds to 23 cc. of the circulation blood and one hundredth of the animal's weight. Muscular exercise is an important factor in the contraction of the spleen. The maximum amount of blood thrown into the circulation by the spleen is much higher in bleeding conditions than that due to exercise. His experiments are then to the effect that the spleen regulates the quantity of the blood in the human body.

B. M. FRIED.

PERIODIC VARIATIONS IN THE SPEED OF CIRCULATION. GOLLWITZER-MEIER, Klin. Wchnschr. **6**:2088, 1927.

According to experiments in animals, changes in the composition of the blood, aroused by a periodic activity in respiration, may initiate periodic variations in the rate of circulation. There is an increase in the minute volume at the end of apnea, and a diminution toward the end of hyperpnea. The variations in pulse volume are in the same direction as those of minute volume, but relatively greater because of a corresponding change in pulse frequency.

AUTHOR'S SUMMARY.

INTERNAL AND EXTERNAL SECRETIONS OF THE PANCREAS. G. DEUSCH and E. DROST, Klin. Wchnschr. **6**:2180, 1927.

There is seldom any disturbance in the excretion of pancreatic juice in patients with diabetes mellitus. The functional tests of the pancreas, as measured by the estimation of the enzymes in the duodenal fluids, do not demonstrate any deviation from the normal. An increase in pancreatic secretion follows the injection of insulin, and apparently is due to the vagus stimulation by the insulin.

AUTHORS' SUMMARY.

ESTERIFICATION OF SERUM CHOLESTEROL IN DISEASE OF THE LIVER. M. BÜRGER and H. HABS, Klin. Wchnschr. **6**:2221, 1927.

In all diseases of the liver in which the flow of bile to the bowel is obstructed, there is a retention hypercholesterolemia. This retention hypercholesterolemia is essentially caused by an increase in the free cholesterol with a relative decrease in the cholesterol esters. Diseases of the liver in which icterus (cirrhosis) is not present may also be accompanied by an increase in serum cholesterol, and the esterification is undisturbed. Cirrhoses of the liver with increase in the serum bilirubin differ. One group is like cirrhosis of the liver without icterus, another is accompanied by a relative, and a third by an absolute, diminution in the cholesterol esters. A complete disappearance of the cholesterol esters from the blood was not observed; therefore, the esterification value of serum cholesterol does not afford a definite conclusion regarding the functional condition of the liver.

AUTHORS' SUMMARY.

RESYNTHESIS OF LACTIC ACID WITH DISTURBANCE OF THE FUNCTION OF THE LIVER. K. BECKMANN, Klin. Wchnschr. **6**:2229, 1927.

With disturbances of the function of the liver in animals as well as in man after the injection of lactates, there is a definite disturbance in the elimination of lactic acid from the blood. These results indicate that similar changes with decompensation of the heart are due to disturbance of the function of the liver because of the stasis.

AUTHOR'S SUMMARY.

HORMONAL STERILIZATION OF FEMALE ANIMALS. L. HABERLANDT, München. med. Wchnschr. **74**:49, 1927.

Female white mice were rendered temporarily and permanently sterile by subcutaneous and oral administration of placental and ovarian preparations. The application to social and sexual hygiene is pointed out but not discussed.

J. D. WILLEMS.

CONTRIBUTIONS TO THE NORMAL AND PATHOLOGICAL PHYSIOLOGY OF THE CEREBROSPINAL FLUIDS III. THE XANTHOPROTEIN CONTENT OF THE BLOOD SERUM AND CEREBROSPINAL FLUID WITH SPECIAL REFERENCE TO RENAL DISEASES AND MENINGITIS. F. LICKINT, München. med. Wchnschr. **74**:448, 1927.

Two hundred and thirty specimens of blood serum and 270 specimens of cerebrospinal fluid were examined for xanthoprotein and indican. The blood serum contains normally from 13 to 28 mg. per cent; the cerebrospinal fluid less than 10 mg. Indican is normally absent from both. In renal diseases, the xanthoprotein value rises and indican appears in serum and fluid. In meningitis, there is a marked rise in the xanthoprotein content of the cerebrospinal fluid.

J. D. WILLEMS.

SUGAR METABOLISM IN TOXIC INSULIN ACTION. F. FISCHLER, München. med. Wchnschr. **74**:680, 1927.

The striated muscles of an animal dead with insulin poisoning are hyperirritable to mechanical stimulation and will contract many minutes after death. Methylglyoxal has the same effect after death, but before death it causes fibrillary muscle spasms which are not affected by anesthetics. Lactic acid and acetone have no such action. The explanation is that insulin causes rapid sugar catabolism which liberates methylglyoxal, and thus the symptoms of poisoning are produced.

J. D. WILLEMS.

FAMILIAL LEUKEMIA. BRÜGGER, München. med. Wchnschr. **74**:683, 1927.

Three infants, sisters, died at the ages of 75, 78 and 105 days of acute lymphatic leukemia, a familial disease, not often seen.

J. D. WILLEMS.

EXPERIMENTS ON THE SECRETION OF THE CEREBROSPINAL FLUID. O. HIRSCH-TABOR and H. VOLLMAR, München. med. Wchnschr. **74**:709, 1927.

The cerebrospinal fluid was drained from rabbits and then the effect of intravenous injection of various substances on the choroid plexus secretion noted. No increase in secretion of fluid followed the injection of extracts of brain and choroid plexus, nor of blood serum and human cerebrospinal fluid with a negative Wassermann reaction. A marked increase occurred with human cerebrospinal fluid with a positive Wassermann reaction.

J. D. WILLEMS.

PHYSIOLOGIC RELATIONSHIP BETWEEN THE APPENDIX VERMIFORMIS AND THE ILEOCECAL VALVE. W. GROSS, München. med. Wchnschr. **74**:1130, 1927.

Faradic stimulation of the exposed musculature of the appendix vermiformia during laparotomy caused isolated contraction of the musculus ileocecalis demonstrating physiologic relationship between that organ and the ileocecal valve.

J. D. WILLEMS.

THE STREAM CURRENTS IN THE ROOT OF THE AORTA, THEIR ACTION AND A NEW MODEL FOR THEIR DEMONSTRATION. M. HOCHREIN, München. med. Wchnschr. **74**:1312, 1927.

A method suitable for the study of the physico-anatomic relations and the functional phenomena of the left cardiac ventricle and the root of the aorta with its value is described. From plaster of paris casts of these organs, a satisfactory, glass-walled model is made, and by means of a fluid containing particles in suspension the blood currents are reproduced and studied. The leaflets of the aortic semilunar valve when at rest, with the pressure equal on both sides of the valve, are widely open; they tend to close with systole, not by any action inherent in the leaflets, but due to whirlpool actions of the blood current in the periphery of the aorta and the sinus of Valsalva. When the central stream in the aorta, flowing distally, stops at the end of systole the leaflets are in contact. The leaflets themselves act only passively. The degree of closure of the valve depends on the pressure of the fluid, the force of the stream, and the rate of flow. There is always a slight physiologic insufficiency of the valve. In a weakly acting heart there may be marked insufficiency without anatomic change. The wall of the sinus of Valsalva is much thinner than that of the aorta, indicating differences in pressure (biologic law of Ernst).

J. D. WILLEMS.

ACUTE INTESTINAL OBSTRUCTION. E. PLATOU, Supplement to Norsk. Mag. f. Laegevidensk., 1927.

The cause of death in ileus is due to absorption of toxic substances from the stagnating intestinal contents. It is assumed that these substances are formed from breaking down of the protein in the contents. The greater the amount of toxic substances absorbed into the circulation the greater the damage to the intestinal wall. After absorption the toxic substances cause an increased metabolism with increased azotemia. This increased azotemia may be of diagnostic and prognostic significance, and all patients with ileus should have from 4 to 6 liters of salt solution every twenty-four hours so long as the azotemia is above normal.

Pathologic Anatomy

CIRSOID ANEURYSM OF THE UTERUS. W. P. GRAVES and G. V. SMITH, Am. J. Obst. & Gynec. **14**:30, 1927.

One patient, aged 62, who had had four pregnancies had severe uterine hemorrhages. Examination with the patient under anesthesia revealed pulsation in the fornices and an enlarged uterus. Light curettage caused severe hemorrhage necessitating an immediate laparotomy. The uterus was pulsated and felt spongy. The specimen when removed showed the myometrium to be riddled with blood vessels and an anterior transverse sinus, and two more near the cornua were seen. The endometrium was thin and atrophied. The muscle was thin subjacent to the mucosa, and then the thickened strata of vessels, both arteries and veins, could be seen.

A. J. KOBAK.

ORIGIN OF RETICULIN FIBRILS. NATHAN CHANDLER FOOT, Am. J. Path. **3**:401, 1927.

In hanging drop tissue cultures of blood, fibrils closely resembling reticulum are formed by disintegration of erythrocytes and rearrangement of the intracellular reticulum. The reticulin fibrils in granulation tissue are not artefacts. At first probably viscid, the fibrils seem to become firm and acquire some tensile strength.

STUDIES OF ENDOTHELIAL REACTIONS: X. ON THE ORIGIN OF THE PULMONARY "DUST CELL." NATHAN CHANDLER FOOT, Am. J. Path. **3**:413, 1927.

The dust cells or "Herzfehlerzell" are probably larger forms of monocytes or blood histiocytes. While the tissue histiocytes may play some part in their production, it is more likely that their ranks are recruited from the circulating monocytes of the blood stream. The origin of these is discussed. The alveolar epithelium of the lung does not produce dust cells in so far as can be ascertained; it possesses totally different affinities for silver salts and can, by means of silver tannate impregnation, be readily recognized and differentiated from the alveolar macrophages, which appear to be of mesenchymal, rather than of endodermal, origin. Furthermore, as has already been pointed out by other investigators, the reactions of these groups to supravital strains are equally divergent. The assumption that there is no nucleated "respiratory epithelium" does not appear to be warranted, for sections supravitally stained with neutral red and counter-impregnated with silver tannate show pictures in every way similar to those drawn by anatomic investigators. As the refractive index of alveolar epithelium is very close to that of glass, it is imperative that

some procedure be used that will render it artificially visible, or that the light in the condenser be arranged so as to utilize the very slightly higher refractive index of the epithelium; otherwise it will escape notice.

AUTHOR'S SUMMARY.

THE ORIGIN OF THE ALVEOLAR PHAGOCYTE STUDIED IN PARAFFIN SECTIONS OF TISSUE STAINED SUPRAVITALLY WITH NEUTRAL RED. LEROY U. GARDNER and DAVID T. SMITH, Am. J. Path. **3**:445, 1927.

The data obtained from a study of the lungs of guinea-pigs stained supravitally with neutral red, immediately after death by air embolism, have suggested the following deductions: The alveolar phagocyte is produced by the desquamation of septal cells. The septal cell belongs to the general group of connective tissue phagocytes or clasmatocytes. These clasmatocytes appear to arise from previously inactive reticulum cells which pass through a monocyte-like phase in the process of maturation. Alveolar epithelium and local vascular endothelium play no part in the origin of the alveolar phagocyte. The arrangement of the neutral red stained cytoplasmic elements is not fixed and cannot therefore be used as a criterion to differentiate clasmatocytes from monocytes.

AUTHORS' SUMMARY.

HYALINE DEGENERATION OF THE ISLANDS OF LANGERHANS IN NONDIABETIC PERSONS. ARTHUR WILLIAM WRIGHT, Am. J. Path. **3**:461, 1927.

Hyaline degeneration of the islands of Langerhans is a lesion which develops commonly in later life and only a small number of cases of diabetes mellitus are ascribable to it. It appears to be the result of slow toxic injury in which the hyaline material gradually accumulates, injures and finally destroys the islet cells, ultimately replacing the insular tissue. Regeneration takes place, but the regenerated tissue, under the influence of the continued action of the injurious agent, is again slowly destroyed. Gradually the regenerative power of the pancreas is worn down, and finally, when so much islet tissue is destroyed that the normal glycolytic hormone can no longer be supplied in sufficient amount, the phenomena of diabetes mellitus appear. These cases may be classed as falling into a prediabetic group, sufficient insular tissue not being involved to bring about the clinical symptoms of diabetes mellitus.

AUTHOR'S SUMMARY.

LOCAL AND SYSTEMIC CHANGES INDUCED BY LIPOID SOLVENTS IN ANIMALS FED ON DIETS VARYING IN VITAMIN CONTENT. LOUIS H. JORSTAD and CHARLES G. JOHNSTON, Am. J. Path. **3**:489, 1927.

Various oils and fats act like coal tar when injected into subcutaneous tissue of animals. All of them dissolve the lipoids of the cell and may be classed as lipoid solvents. The cellular activity about droplets of various lipoid solvents injected into the subcutaneous tissue of rats is greatly increased by feeding a diet rich in vitamin A. The lipoid solvent remains en masse in an animal fed a ration deficient in vitamin A and disperses into smaller droplets in the animal fed a ration rich in vitamin A. The tissue reaction about the lipoid solvent is altered in degree if the fats are removed from the solvent with ether before it is injected into the tissue. Rats injected subcutaneously with certain lipoid solvents or mixtures of them and fed a diet rich in vitamin A suffer a massive fatty infiltration of the liver. This infiltration occurs at different periods of time after the injection of the different lipoid solvents.

Chloroform produces a necrosis of the liver because it diffuses rapidly throughout the system. This lesion is similar to that produced locally by coal tar in the tissue.

AUTHORS' SUMMARY.

THE INVOLVEMENT OF THE AORTIC VALVE IN SYPHILITIC AORTITIS. O. SAPHIR and R. W. SCOTT, Am. J. Path. **3**:527, 1927.

The earliest lesion of syphilis of the aorta is an obliterative endarteritis of the vasa vasorum. The term "mesaortitis syphilitica" therefore gives an erroneous conception of the disease and "aortitis syphilitica" seems more appropriate. Necrosis of the media is probably secondary and attributable to nutritional disturbances. The changes of the aortic valve due to syphilis are characterized grossly by adhesions between the lateral parts of the leaflets and the aortic intima, leading to a separation of the commissures. The formation of hyaline plaques in this area is secondary. Histologically the affected parts of the leaflets and the aortic wall of the sinus of Valsalva show first degenerative and later chronic inflammatory changes.

AUTHORS' SUMMARY.

THE SPLEEN IN WEST AFRICAN YELLOW FEVER. OSKAR KLOTZ and WINIFRED SIMPSON, Am. J. Path. **3**:569, 1927.

The malpighian bodies show a marked disappearance of their lymphoid elements, while the endothelial cells within them appear more numerous. In the early stages of the reaction, the germinal centers of the malpighian bodies may show some hyperplasia of their endothelial cells, which is soon followed by a hyaline degeneration and necrosis. The lymphoid follicles tend to disappear, and in their peripheral portions the endothelial cells in the sinusoids become free. These cells tend to enlarge and form irregular multinucleate masses. During the degeneration of these endothelial cells, the chromatin of the nuclei becomes scattered through the cytoplasm and not infrequently resembles protozoan parasites. In the pulp spaces at some distance from the lymphoid follicles the tissues are injured, but definite hyperplasia of the cells of the reticulo-endothelial system cannot be made out. In those cases in which the spleen has been severely affected, debris arising from the dead endothelial cells can be discerned in the sinusoids. The reaction, although not a specific one for yellow fever, assists the physician in making a differential diagnosis from other diseases which in the tropics may simulate it. It is distinctive from that which arises in relapsing fever and in infectious jaundice.

STUDIES IN THE PATHOLOGY OF RHEUMATIC FEVER: TWO CASES PRESENTING UNUSUAL CARDIOVASCULAR LESIONS. ALVIN M. PAPPENHEIMER and W. C. VON GLAHN, Am. J. Path. **3**:583, 1927.

It has not been thought necessary to review again the literature dealing with rheumatic vascular disease, since this has been adequately covered in previous papers and in the recent admirable summary by Sacks. We have found a few references to the occurrence of verrucous lesions on the intima of the aorta and, in one instance (Heydloff), in the innominate and carotid arteries. In one of the best described cases, that of Barbacci, these lesions began 1 cm. above the sinus of Valsalva and histologically were not unlike the organizing verrucae of rheumatic endocarditis. Bacteria could not be demonstrated in them. The heart was normal. It is quite possible that some of the cases were rheumatic in origin, though no reference is made to this possibility by the authors. Neither are the histologic descriptions sufficiently detailed to

justify any definite conclusions. It must be remembered, however, that these papers antedated the recognition of the specificity of the lesions in rheumatic cardiac disease. While many of the older writers, and particularly French authors, have ascribed to the "rheumatic virus" an important place in the causation of arterial disease, the connection was based on clinical inference rather than histologic specificity. The recent studies on the auricular lesions have made it apparent that the rheumatic infection may be evidenced by a diffuse response as distinctive in its cellular composition and arrangement as is the Aschoff nodule or the endocardial verruca. It is therefore not surprising that one may find this specific type of reaction not confined to the heart, but taking place also in the lining of the aorta and the larger arteries. The detailed study of these cases brings evidence of this fact. Such evidence is of necessity indirect and based chiefly upon the analogy of the lesions in the blood vessels with those admittedly of rheumatic origin occurring in the auricular endocardium. Until the specific agent shall have been finally identified and similar lesions experimentally produced, this is as far as one can go. The lesions which have been depicted in the aorta are, in these cases, not mere extensions from the aortic valves, since they occurred at a distance, indeed in the second case, in the midthoracic portion. The aortitis is of two types, which may be associated or occur discretely, and which probably corresponds to the route of infection. When this takes place from the lumen, there is produced a diffuse reaction in the intima and subjacent media, comparable to that which so frequently affects the auricular endocardium. On the other hand, infection reaching the aortic wall via the vasa vasorum produces a focal perivascular reaction, more closely analogous to the Aschoff nodules about the small branches of the coronary vessels. It is not maintained that this difference in type of reaction is of fundamental importance; it may be in part dependent upon the peculiarities of the structural arrangement of the tissue in which the reaction is occurring. It seems to us, however, of importance to recognize the fact that the pathology of rheumatic infection does not begin and end with the Aschoff nodule. Experience has taught us to recognize as equally distinctive the more diffuse reaction whether it occur in the valves, endocardium, aorta or the smaller visceral vessels. AUTHORS' SUMMARY.

A CONTRIBUTION TO THE PATHOLOGY OF GENERALIZED ARGYRIA WITH A DISCUSSION OF THE FATE OF SILVER IN THE HUMAN BODY. A. O. GETTLER, C. P. RHOADS and SOMA WEISS, Am. J. Path. **3**:631, 1927.

Argyria may be caused by organic or inorganic silver compounds. Silver from organic preparations like argyrol and collargol may be absorbed from the gastro-intestinal tract. General argyria shows itself first on the gums and buccal mucosa, and in bluish discoloration. Here should be a warning against further use of silver. A case of severe general argyria is described, and the total amount of silver in the body is estimated at from 90 to 100 Gm. There were no definite indications that the silver caused any disturbance except discoloration. The silver occurred in granules along and between bundles of collagen and elastic fibers and also in cells in the spleen and lymph nodes.

A CASE OF PRIMARY MESENCHYMAL HEPATOMA WITH NECROPSY. NATHAN CHANDLER FOOT, Am. J. Path. **3**:653, 1927.

A case of multiple tumors, occuring in a boy of 4, is described from the clinical and pathologic points of view, the latter being stressed. The tumors simulate multiple granulomas, possibly tuberculous or syphilitic, but

when examined more closely are found to be neoplastic. They are rich in reticulum and are found to invade almost all the periportal tissue of the liver. Similar cells and reticulum are found in the neighboring costal bone marrow, which are probably metastases to that tissue, although this is not proved. The nature of the growth is discussed, and it is concluded that it probably had its origin in the mesodermal primordium of the liver; the possibility of its being of epithelial origin has not been overlooked.

AUTHOR'S SUMMARY.

SARCOSPORIDIAL INFECTION OF THE MYOCARDIUM IN MAN. SAMUEL W. LAMBERT, JR., Am. J. Path. **3**:663, 1927.

There were no symptoms during life which could be referred to this infection. As all the tissue was preserved before the microscopic sections were examined, it was not possible to carry out any experimental work on the transmission of this parasite. However, it seems quite probable that it is some form of sarcosporidia, and in a rather early stage of its development, judging from the fact that no capsule can be seen surrounding the cyst. It differs from the majority of species previously described in the following characteristics: In the absence of a surrounding membrane; in the lack of demonstrable septa dividing the cyst into compartments, and in the measurements, which though not carried out on fresh material, indicate that this form is smaller than those previously described. As no sections of skeletal muscle were taken for microscopic examination it is not known whether this infection was general throughout the whole body or merely confined to the myocardium. The case is reported as one of probable sarcosporidial infection of man, and is the second one on record in which the protozoa invaded the heart muscle.

AUTHOR'S SUMMARY.

OBSERVATIONS ON PEPTIC ULCER: I. A METHOD OF PRODUCING CHRONIC GASTRIC ULCER. II. X-RAY STUDY OF EXPERIMENTAL CHRONIC ULCER. III. HEALING OF EXPERIMENTAL PEPTIC ULCER AFTER GASTRO-ENTEROSTOMY. C. B. MORTON, Ann. Surg. **85**:207, 1927.

By way of introduction, Morton summarizes the differential points between acute and chronic ulcers, the various theories regarding the etiology of the chronic ulcer and the various more or less successful experimental methods of producing a chronic ulcer or of delaying healing in an acute ulcer. Morton was able to produce a chronic ulcer in dogs by first causing an acute ulcer and then performing surgical duodenal drainage, as described by Mann and Williamson. The ulcers produced by simple excision of gastric or duodenal mucosa healed in two weeks, those in the lesser curvature near the pylorus somewhat slower than those on the fundus or greater curvature. All dogs on which only surgical duodenal drainage had been performed developed jejunal ulcers. The group in which excision of mucosa and surgical duodenal drainage were performed at the same operation showed definite delay in healing; in some cases the ulcers took on the characteristics of a subacute and chronic peptic ulcer. The delay in healing was much more marked in the lesser curvature. The results were the same when the duodenal drainage was performed two weeks after the primary excision of gastric mucosa.

Morton describes, too, the roentgenologic observations in a normal stomach of a dog and then reports the observations after surgical duodenal drainage had been performed and had given rise to chronic jejunal ulcers. Three large ulcers were depicted and two subacute ones suspected. After the ulcer had formed, some delay in the emptying time occurred.

Chronic jejunal ulcers were first formed by duodenal drainage, and gastro-enterostomy was done later. The amount of healing following the latter operation was in direct proportion to the size and degree of chronicity of the ulcer. New ulcers, however, formed in the efferent loop of the anastomosis. Gastro-enterostomy merely supplied an accessory outlet for the acid chyme, thereby decreasing the amount and force of the ejection from the pylorus, thus relieving the original ulcer from the degree of trauma it had been subjected to in its development.

N. ENZER.

FAT NECROSIS OF THE BREAST. A STUDY OF 20 CASES. J. GOTTESMAN and A. P. ZEMANSKY, Ann. Surg. **85**:438, 1927.

The authors did not find any evidence that trauma was an etiologic factor in the production of fat necrosis. From its frequent association with inflammation and cystic disease of the breast, they suggest the possibility of the necrosis resulting from irritation due to degeneration of fatty material escaping from dilated ducts. They describe and tabulate the results in twenty cases.

N. ENZER.

METACARPAL CENTRAL GIANT-CELL TUMORS. E. DUSKES, Ann. Surg. **85**:912, 1927.

A case report is given of a centrally placed benign giant cell tumor in the metacarpal bone on the third finger of the left hand.

N. ENZER.

THE ARTERIOLAR LESIONS OF GLOMERULONEPHRITIS. ARTHUR M. FISHBERG, Arch. Int. Med. **40**:80, 1927.

The arterioles of various organs were studied in thirty-seven cases of diffuse glomerulonephritis. The arteriolar lesions of diffuse glomerulonephritis are of four histologically and pathogenetically distinct varieties: Acute necrotizing arteritis was found in the renal arterioles in three of eight patients dying during the acute stage of diffuse glomerulonephritis. These lesions are probably of the same (toxic?) origin as the glomerular lesions. Endarteritis obliterans was present in seventeen of twenty-nine cases of chronic diffuse glomerulonephritis in various stages. Endarteritis obliterans was not found in the early stages or often in the end stage (secondary contracted kidney); it occurred predominantly in those patients who succumbed after the process had lasted for some years, but while the inflammatory process in the glomeruli was still active. The histology of the lesion is identical with that seen when an artery is ligated, and the opinion is advanced that the endarteritis obliterans is due to the glomerular lesion blocking the blood current. Arteriosclerosis similar in histology and distribution of the lesions to that found in essential hypertension was present in all twelve cases of secondary contracted kidney. It was not found in early cases and was of but slight degree in the moderately advanced cases. The occurrence of arteriolosclerosis is correlated with hypertension of long duration. Muscular hypertrophy in the media of the renal arterioles was well marked in many cases of chronic glomerulonephritis of considerable duration but still "active." It was not found in the early stages. In cases of secondary contracted kidney of many years' duration the medial muscle usually atrophies as it does in essential hypertension. The fact that arteriosclerosis of the same histology and distribution as that found in essential hypertension occurs in chronic glomerulonephritis of long duration is strong added evidence that this lesion is a consequence of the hypertension.

AUTHOR'S SUMMARY.

HEMATOLOGY OF SUBACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS. O. H. PERRY PEPPER, J. A. M. A. **89**:1377, 1927.

Anemia is the rule when the disease is of long duration; it tends to increase toward the end and may become very severe. It is always of a chloro-anemic type. The leukocyte count tends to stay within normal limits or a little above, but high leukocytosis, usually with a high polymorphonuclear percentage, readily arises on the occurrence of infarction, thrombosis or other complication. A great increase in the circulating monocytes and the presence of many macrophages, while occasionally seen in other diseases, is strongly suggestive of bacterial endocarditis but is not peculiar to *Streptococcus viridans* endocarditis. More platelet counts are needed to confirm or disprove the occurrence of thrombopenia.

AUTHOR'S SUMMARY.

THE CARDIOVASCULAR RESPONSE IN EXPERIMENTAL NEPHRITIS. F. W. HARTMAN, J. A. M. A. **89**:1936, 1927.

Sclerosis and obliteration of the small arterioles along with replacement of the tubular epithelium and hyalinization of the glomeruli in the kidney are induced by deep irradiation. Hypertrophy of the left ventricle of the heart and hypertension follow the induction of such a lesion in the kidney. These experimental data tend to sustain the contention of Romberg, Fahr and others that the kidney may be directly responsible for a certain group of cases of cardiac hypertrophy and hypertension.

AUTHOR'S SUMMARY.

ACTION OF OILS IN MUSCLE TISSUES. LOUIS H. JORSTAD and FRANK H. GLENN, J. A. M. A. **90**:26, 1928.

Oils injected into the muscle tissue of white rats localize in the connective tissue around the muscle bundles and form masses that tend to remain a long time.

THE INFLUENCE OF HIGH TEMPERATURE ON THE GUINEA-PIG TESTS: HISTOLOGICAL CHANGES AND EFFECTS ON REPRODUCTION. W. C. YOUNG, J. Exper. Zool. **49**:459, 1927.

Following the application of warm water to the scrotum of the guinea-pig sufficient to destroy the germinal tissue in one application, testes were removed at frequent intervals from one hour to one year after the treatment and studied histologically. In addition, twenty males were given opportunities to mate at intervals of five to ten days for approximately four months after the treatment.

Chromolysis and liquefaction of the germinal elements begins immediately and continues for twelve days, by which time a complete evacuation of germinal elements except spermatogonia occurs. The order of germ-cell degeneration is large primary spermatocytes, secondary spermatocytes and young spermatids first; and subsequently older spermatids, spermatozoa and young primary spermatocytes. Spermatogonia are the most resistant of all germinal elements. Sperm contained in the epididymis are likewise very resistant.

Recovery of spermatogenetic function occurs whenever spermatogonia survived. Regenerative changes are apparent fifteen days after treatment, and sperm are again produced by the forty-fifth day.

Changes in reproductive capacity are readily identifiable with histologic changes. The frequency of sterile matings, increased gradually until approximately 75 per cent of the matings made between the thirtieth and the seventy-

fifth day were sterile. Reproductive capacity was then usually regained. Whether stillbirths and abortions occurring in the course of the breeding histories are attributable to the heat injury or to some other factor has not been determined.

AUTHOR'S SUMMARY.

SOME PATHOLOGIC FORMS OF CORPUS LUTEUM. W. SHAW, J. Obst. & Gynec. Brit. Emp. **34**:300, 1927.

In discussing the various pathologic forms of corpus luteum, Shaw dwells particularly on cysts having tarry fluid and lutein cells in their walls. The types described are tarry theca lutein cysts, tarry granulosa lutein cysts and tarry corpus luteum cysts. The first two are derived from atretic follicles; in the first, only the theca lutein cells undergo luteinization, while in the second theca and granulosa both develop lutein cells. The lutein cells are large, with a deep, brownish pigment, and have a mosaic arrangement. The tarry corpus luteum is derived from the true corpus luteum, the characteristics of which it has. In all three, the tarry fluid is derived from degenerated red blood cells. The cysts develop a heterotopic epithelial lining which originates from endothelial cells by a process of metaplasia. The lutein cells later may disappear and be replaced by hyaline tissue. The epithelium persists and differs from that of endometrial cysts by the lack of an underlying stroma. The cysts may rupture and become implanted on adjacent organs. Their etiology is unknown, and there are no evidences of inflammation. Shaw suggests they may be related to disturbances in the ductless glands.

A. J. KOBAK.

CYSTADENOMA PSEUDO-PAPILLIFERUM MALIGNUM OF THE KIDNEY WITH METASTASES IN THE TONGUE. DAVID W. MACKENZIE and T. R. WAUGH, J. Urol. **18**:331, 1927.

A case is described.

TRUE HERMAPHRODITISM IN MAN: REPORT OF A CASE WITH A CRITICAL REVIEW OF THE LITERATURE. BORIS KWARTIN and JOSEPH A. HYAMS, J. Urol. **18**: 363, 1927.

A case of hermaphroditismus verus unilateralis completus femininus sinister in a colored person is reported.

INFARCTION OF THE TESTICLE. SAMUEL LUBASH, J. Urol. **18**:421, 1927.

An instance of infarction of the testicle in a man, aged 30, is described. The infarction seemed to develop on the lifting of a heavy set of tools above the head when sudden pain in the left testicle developed. A triangular necrotic area was found in the testicle surrounded by a hemorrhagic and leukocytic border. It is suggested that the infarction developed following a temporary torsion of the cord.

SPONTANEOUS RUPTURE OF THE SPLEEN. M. P. SUSMAN, Brit. J. Surg. **15**:47, 1927.

In the case reported, as well as in six others collected from the literature, the spleen was thought to be normal, but the probability of previous damage having been present, evidence of which may have been destroyed at the time of rupture, is considered.

BENSON BLOOM.

POLYPI OF THE INTESTINE, WITH SPECIAL REFERENCE TO THE ADENOMATA. J. H. SAINT, Brit. J. Surg. **15**:99, 1927.

In the small intestine, the most common type of polyp is the glandular hyperplasia of the mucosa overlying excessive lymphoid tissue. A case of hemangioma, one of carcinoid and one of lipoma are also reported. Adenomas, while rare in the small intestine, form the commonest type of polyp in the large intestine. In three adenomas of the large intestine, malignant changes were found, but the author does not believe that carcinoma of the colon ordinarily arises from an adenoma.

BENSON BLOOM.

SOME GENERAL DISEASES OF THE SKELETON. H. A. T. FAIRBANK, Brit. J. Surg. **15**:120, 1927.

Fairbank discusses briefly a number of interesting skeletal diseases, including among others osteogenesis imperfecta, dyschondroplasia, achondroplasia, osteomalacia and osteitis deformans. The paper is well illustrated with a number of roentgenograms.

BENSON BLOOM.

A CASE OF "WANDERING SPLEEN" CAUSING INTESTINAL OBSTRUCTION. H. A. H. HARRIS, Brit. J. Surg. **15**:163, 1927.

The spleen was impacted in the pelvis and attached by a long pedicle containing the tail of the pancreas.

BENSON BLOOM.

ON CERTAIN ABNORMAL CONDITIONS OF THE MACULAR REGION USUALLY CLASSED AS COLOBOMAS. IDA C. MANN, Brit. J. Ophth. **11**:99, 1927.

Colobomas of the macular region are classified into three main types: (*a*) pigmented macular colobomas, involving choroid only; (*b*) nonpigmented macular colobomas, involving retina as well, and (*c*) macular colobomas associated with abnormality of blood vessels. This is the rarest form.

The discussion is then taken up as to whether colobomas are developmental or pathologic changes. The three possibilities in the developmental theories are: (*a*) coloboma macula may be due to an anomaly of growth of the whole cup; (*b*) it may be due to a localized anomaly of differentiation of some of the pluripotential cells of the walls of the optic cup, that is, the primary fault may be in the neurolectoderm; or (*c*) it may be due primarily to a defect in the development of the mesoderm surrounding the optic cup. Embryologic evidence is shown to be opposed to all three theories.

The pathologic theories are then considered. They are: (*a*) coloboma macula may be the result of a hemorrhage at birth; (*b*) it may not be truly congenital, but may have resulted from a choroiditis in infancy, and so fall in line with other cases of postnatal inflammatory macular disease, and (*c*) it may be the result of an intra-uterine choroiditis.

The first two theories were dismissed because sufficient data were not forthcoming to prove or disprove them. The author believes that the theory that macular coloboma is due to intra-uterine choroiditis affords the best explanation of the condition so far put forward, and only by accepting this theory can all the types of so-called macular choroiditis be brought under one heading. The exact type of defect produced depends on: (*a*) the time during development at which the lesion occurred, and (*b*) the nature of the inflammation, i. e., whether destructive or irritative.

The diagnostic tests to be applied are: 1. The presence of normal retinal vessels over the defect; this points to an irritative condition after the sixth

month; 2. the presence of ectasia or absence of retinal vessels; this points to a more destructive process, with or without an earlier onset, from the fourth to the fifth month; 3. the persistence of one of the vasa hyaloidea propria; this is diagnostic of a process occurring before the end of the third month.

BENJAMIN RONES.

A STUDY OF SOME CASES OF PRESENILE ARTERITIS. P. MOULONGUET and P. PAVIE, Ann. d'anat. path. **4**:685, 1927.

The authors report five observations of arteriosclerosis occurring in young persons. In one case, the disease occurred in a Jew of Russian origin, and the histology of the arterial lesion was that of a thrombo-angiitis obliterans as described by Buerger. The authors affirm that peripheral gangrene found in juvenile or presenile patients is met with in different conditions and that they must be differentiated. In their experience, they could identify the thrombo-angiitis obliterans of Buerger, arterial syphilis and precocious arteriosclerosis.

B. M. FRIED.

THE PROBLEM OF AMYLOSIS: GENERAL REVIEW. CHARLES OBERLING, Ann. d'anat. path. **4**:733, 1927.

Oberling reviews recent German work on the pathogenesis of amyloid formation in the body. From chemical investigation, it seems that on the whole the genesis of amyloid and connective tissue is subordinated to the same laws, and that amyloid may be considered as an abnormal "fundamental substance." It is, therefore, erroneous to speak of amyloid "degeneration," because the formation of amyloid is no more degenerative than the formation of collagen.

The genesis of amyloid, which is apparently a protein, is due to two factors: (1) a general factor which consists in an increase of the globulins in the circulating blood, and (2) a local one which leads to the transformation of the cellular globulins into amyloid.

B. M. FRIED.

AN ANATOMICO-CLINICAL NOTE ON THREE CASES OF ACUTE DELIRIUM. H. CLAUDE and J. CUEL, Encéphale **22**:628, 1927.

The acute delirium or the delirium grave or the acute delirious mania of the older authors is discussed. The symptomatology is a combination of hallucinations, extreme agitation, fever, rapid emaciation and sitophobia, which means a fear of taking food. The condition almost invariably takes a fatal course. The sitophobia seems to be due to a fear of being poisoned. All three patients died within from two to three weeks.

At autopsy, the thoracic and abdominal organs were congested but without specific lesion. The brain was also in extreme congestion, and the parenchyma showed a violet discoloration. A focal lesion or a meningeal exudate was not present. Microscopically, there was an abundance of newly formed capillaries, but the walls of the blood vessels were neither thickened nor infiltrated. The Nissl stain revealed diminished stain ability and a moderate degree of satellitosis and neuronophagia. With sudan a considerable accumulation of lipoids was found in the ganglion cells of practically all cortical areas. The cerebellum and brain stem were hardly affected. Chromatolysis, karyolysis, fatty degeneration, satellitosis and neuronophagia were reported as the main characteristics by Anglade and Ladame. The present cases confirm their observations. The majority of cases reported in the literature occurred in women. The changes point to an infectious—toxic agent. Ladame explains the condition on the

basis of a disturbance of the permeability of the cell membrane. A general lipoidolysis occurs. If, then, the lecithin of the cell membrane is also dissolved, a fatal disturbance of its permeability results.

A. Low.

The Regeneration of Striated Muscle After Enervation. G. Calissano, Arch. per le sc. med. **49**:683, 1927.

The enervation of a muscle does not diminish entirely the formative reaction caused by an incision, and the regressive occurrences which one verifies at a distance from the operation are attributed to atrophy and to consecutive degeneration to the tearing away of the nerve. The interruption of a nerve followed by regeneration does not modify the course of cicatrization of the incision in muscle which satifies that nerve, even if the incision was made before the regeneration was complete.

A. J. Salle.

Amyloid of the Conjunctiva. I. Wallgren and M. Vannas, Arb. a. d. path. Inst. d. Univ. Helsingfors. **4**:211, 1926 (new series).

A laborer, aged 21, who had had thickening of the eyelids and impaired vision, especially in the left eye, since the age of 9, submitted to eight operations before coming under the observation of the authors. A diagnosis of amyloid degeneration and trachoma of the lids of both eyes was made. Microscopically, the glassy material extirpated from the conjunctivae and lymph glands gave chemical reactions typical for amyloid and was disposed in the usual way about the blood vessels. The connective tissue network about the blood vessels and tarsal glands was undisturbed, as demonstrated by silver impregnations. The unusual feature in this patient was the deposition of amyloid in the parotid and submaxillary lymph glands. The inguinal lymph glands were free from such deposits. A second patient, a woman, aged 38, who had had a swollen left upper eyelid for nineteen years and trachoma, also was relieved of amyloid deposits in the conjunctiva. The authors do not think trachoma is a necessary predisposing factor in conjunctival amyloid deposition, although they failed to find other diseases to account for the condition in their patients. They are cognizant of observations that amyloid of the conjunctiva is seen most frequently in regions in which trachoma is prevalent.

George Rukstinat.

Pigment Deposits in the Gallbladder Wall of Inebriates. A. Priesel, Centralbl. f. allg. Path. u. path. Anat. **40**:181, 1927.

Finely granular brownish-yellow material was found in the gallbladder musculature of heavy drinkers in two operative and three autopsy specimens. The pigment deposits were heaviest near the mucosa, and in all instances were confined to the region of the nucleus. It resembled, microscopically and in its chemical behavior, melanin and the pigment found in the circular muscle layer of the upper small bowel in persons who use alcohol excessively. The granules were resistant to the action of acetic and mineral acids and alkalis; gave negative Gmelin and iron reactions; resisted bleaching with potassium permanganate and oxalic acid for from twenty-four to forty-eight hours and even then persisted as light yellow masses; were indifferent to fat stains such as scharlach R and sudan III; were insoluble in ordinary fat solvents; stained a dirty black-green with nile blue sulphate and neutral red and retained silver nitrate as large brownish-black dots. The author considers this an endogenous

pigment, the result of some metabolic reaction. Autopsy material was not entirely satisfactory as bile staining of the muscle obscured the pigment granules.

GEORGE RUKSTINAT.

PERINEPHRITIS CAPSULARIS HEMORRHAGICA. P. HEILMANN, Centralbl. f. allg. Path. u. path. Anat. **40**:185, 1927.

The right kidney of a man, aged 64, which was removed at operation, was surrounded by a huge hematoma which had dissected away and to some extent infiltrated the fatty capsule. The fibrous capsule was fibrillated in places, the outer strands extending into the hematoma; in other places it was hemorrhagic. Microscopically, a thin layer of parallel connective tissue cells entirely covered the kidney, and on these the hematoma rested. Thin-walled, distended vessels ran from the fibrous capsule into the blood clot and were surrounded by a ring of leukocytes. The impression was that these were the result of a slowing of the blood stream, with diapedesis of red and white blood cells. Neither the capillaries nor their endothelium were increased, and the only alteration in the connective tissue in general was a spreading apart of the fibers by blood.

Ricker suggests that such bleeding may be due to loss of vasomotor function followed by diapedesis. The author thinks some toxic influence (autointoxication) causes injury to the blood vessel and is followed by diapedesis. An explanation is not offered for the specific attack on the renal vessels, but allusions are made to the mildest grade of internal hemorrhagic pachymeningitis as running a close parallel. The condition is also probably related to the so-called perirenal hygroma of Fahr.

GEORGE RUKSTINAT.

CEREBRAL VEIN RUPTURE IN POISONING WITH ILLUMINATING GAS. E. PETRI, Centralbl. f. allg. Path. u. path. Anat. **40**:385, 1927.

Serial sections of a cerebral medullary vein in the body of a man dying four days after poisoning with illuminating gas disclosed the following: The connective tissue fibers of the vessel wall were split apart, swollen and formed a glassy, homogeneous nucleus-poor mass bordering on a rent involving all coats. Near the tear was an extensive intramural and extramural round cell infiltration indicating that the process existed during life. The defect in the vessel wall was tightly sealed with a fibrin plug which prevented escape of blood. Several similar ruptures were found in various parts of the brain, but the author was not able to demonstrate a connection between these and hemorrhages into the brain substance.

GEORGE RUKSTINAT.

CONGENITAL ABSENCE OF BOTH INFRARENAL GLANDS? W. VOIGHT, Centralbl. f. allg. Path. u. path. Anat. **40**:387, 1927.

A woman, aged 43, whose first child died of convulsions at the age of 10 weeks, whose second pregnancy resulted in a stillbirth and whose third pregnancy resulted in a miscarriage, entered the hospital with the clinical signs of Addison's disease, a strongly positive Wassermann reaction and two indolent ulcers of the left knee. Evidences of status lymphaticus were found at autopsy, although the thymus was atrophic. Both suprarenal glands were missing, as were also their arteries from the usual sources. Small nodules of suprarenal cortical tissue were found adhering to the upper poles of the kidneys, and in some of these were masses of central fibrous connective tissue heavily infiltrated with round cells. The ulcers of the knee were thought to be syphilitic, but there were no other evidences of syphilis in the body. The possible expla-

nations for the observations are: first, that some disease possibly syphilis caused atrophy of the suprarenal glands, although in such an event the process must have been marked to destroy completely all vessels; and second, that other chromaffin-possessing cells such as those of the sympathetic nervous system, carotid body, etc., took on the function of the suprarenal medulla but finally failed to supply the insufficiency because of a failure to hypertrophy.

GEORGE RUKSTINAT.

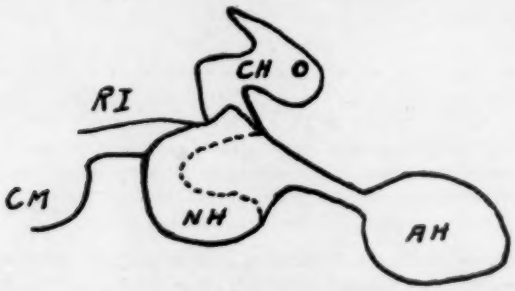
A PAPILLARY MYXOMA OF THE RIGHT AURICLE. B. UGRIUMOW, Centralbl. f. allg. Path. u. path. Anat. **41**:7, 1927.

A girl, aged 15, died of cardiac decompensation. At autopsy, both leaves of the pericardial sac were grown together. The right auricle was almost entirely filled with papillary, grapelike clusters of red-gray, jellylike material, over all 7.5 cm. in diameter attached by a wide stalk to the site of the foramen ovale. Several papillae extended past the tricuspid ring and were attached to the leaflets and papillary muscles of the tricuspid valve. Microscopically, the centers of the papillary masses consisted of fresh blood surrounded by lymphocyte-like cells and a few plasma cells, but the stellate cells characteristic for a myxoma were not found.

GEORGE RUKSTINAT.

DYSTOPIA OF THE NEUROHYPOPHYSIS. H. HAMPERL, Centralbl. f. allg. Path. u. path. Anat. **41**:97, 1927.

At the autopsy of a man, aged 69, dying from a strangulated hernia, a hemispherical, granular, brown, mass 8 mm. broad and 4 mm. high occupied the site of the infundibulum. This was composed of typical neurohypophysial elements with the exception of a thin rim of anterior lobe structures on the front edge which were continuous with similar glandular strands in the stalk.



Schematic representation of anomaly. The left side of the picture represents the posterior side; the right, the anterior and the top, the cephalad. The letters *AH* indicate adenohypophysis; *CH O*, optic chiasma; *CM*, corpus mammillare; *NH*, neurophypophysis and *RI*, recessus infundibuli.

The stalk, 3.5 mm. in length and 2 mm. in diameter, was highly vascular in its central part and continuous anteriorly with the adenohypophysis in the sella turcica. According to Hochstetter, such an anomaly is produced by interruption in the development of the neurohypophysis between the 20.9 and 29.7 mm. stage in embryonic life.

GEORGE RUKSTINAT.

ENCEPHALITIS ACUTISSIMA. J. L. ECKEL, Jahrb. f. Psychiat. u. Neurol. **45**:7, 1926.

The author describes a rapidly fatal case which revealed microscopically a meningeal and perivascular leukocytic infiltration spreading into the parenchyma of the brain. Many ringlike perivasal hemorrhages were found. A toxic basis is suggested.

ROY GRINKER.

PONTILE HEMORRHAGE. M. L. RICHARDSON, Jahrb. f. Psychiat. u. Neurol. **45**:298, 1927.

A sharply defined pontile hemorrhage is described revealing microscopically a marked cerebral edema in the vicinity. The aqueduct was compressed giving rise to a hydrocephalus. A secondary lymphocytic infiltration of the adjacent vessels was found.

ROY GRINKER.

THE PATHOLOGIC ANATOMY OF EGYPTIAN MUMMIES. A. SACK, München. med. Wchnschr. **74**:372, 1927.

This is a résumé of reports by other authors on 30,000 mummies. Only unquestionable pathologic conditions are considered. There are two mummies with tuberculosis of the spine; two with osteosarcoma; one with a harelip; one with club feet; one with gout; one with leprosy; two with stones in the urinary bladder; three with stones in the kidney; one with stones in the gallbladder; one with a pelvic abscess; one with a decubitus ulcer; one with appendicitis; one with smallpox scars, and many with fractures, carcinoma, dental caries, arthritis with bone changes, mastoiditis and calcification of the arteries. There is no mummy with syphilis of the bones.

J. D. WILLEMS.

JUVENILE CIRRHOSIS OF THE LIVER. D. KIRSCHENBLATT, München. med. Wchnschr. **74**:856, 1927.

A boy, aged 14, after malaria of three years' duration developed a Laennec cirrhosis of the liver. The viscus was rough and hard, and extended to the umbilicus.

J. D. WILLEMS.

CONSTITUTIONAL EOSINOPHILIA. E. SMITS, München. med. Wchnschr. **74**:896, 1927.

A young Japanese with malaria has an eosinophilia of 30 per cent which has persisted for several years after he is entirely well. An explanation is not given.

J. D. WILLEMS.

TUMORS OF THE CAROTID BODY. H. FLÖRCKEN, München. med. Wchnschr. **74**:931, 1927.

A hard tumor the size of a fist was removed from the right side of the neck of a woman, aged 34. During operation, ligation of the common carotid artery was necessary. The tumor histologically proved to be a carcinoma of the carotid body.

J. D. WILLEMS.

HEMOLYMPHANGIOMA OF THE BREAST. H. U. KALLIUS, München. med. Wchnschr. **74**:1016, 1927.

A woman, aged 26, had a soft, conglomerate multicystic mass in the right breast. All cysts fluctuated and contained fluid, some red to blue, others yellow to colorless. The largest cyst was the size of a fist. Histologically, the mass was a mixed cavernous hemangioma and lymphangioma.

J. D. WILLEMS.

THE APPEARANCE OF RIGOR MORTIS AS DETERMINED BY EXPERIMENTS ON RABBITS. L. WACKER, München. med. Wchnschr. **74**:1041, 1927.

Rabbits were killed by starvation, by strychnine, by carbon dioxide gas, and by exsanguination with and without urethan narcosis, and the time interval between the moment of death and the beginning of rigor mortis was established. There was a decrease from four hours when the muscle had been at rest prior to death to two minutes when it had been in fatigue. Analysis of the muscle for lactic acid and phosphates (buffer substances) showed maximal amounts of both when the time interval was greatest.

J. D. WILLEMS.

SECONDARY MYELOSIS IN TUBERCULOSIS. B. SWIRTSCHEWSKAJA, Virchows Arch. f. path. Anat. **262**:1, 1926.

The author reports a case of tuberculous polyserositis, caseous tuberculous endometritis and salpingitis, and miliary tuberculosis in a woman, aged 45. During the two months before her death the erythrocyte count varied from 2,300,000 to 3,900,000 with hemoglobin percentages of from 35 to 55 per cent. The leukocytes ranged from 10,500 to 33,250, myelocytes, myeloblasts and metamyelocytes together constituting from 12.1 to 30.5 per cent of the total, and monocytes from 3.3 to 13.7 per cent. Lymphoid hyperplasia was present in the bone marrow, and myelo-erythropoiesis was noted in the spleen. Eighteen previously reported cases of tuberculosis with myelosis are briefly reviewed, and discussed at greater length, in relation to the case reported and to idiopathic leukemia. The myelosis in tuberculosis is similar to that described in a number of other infectious diseases and to that of leukemia, the latter differing only in that the changes are more marked and usually of longer duration. Since the cause of leukemia is unknown, the author concludes that the myelosis of leukemia may also be secondary, to some factor as yet unknown, and that histopathologically, no distinction can be made between idiopathic and secondary myelosis.

O. T. SCHULTZ.

LIPOID DEPOSITION IN THE MITRAL VALVE. A. M. TROITZKAJA-ANDREEWA, Virchows Arch. f. path. Anat. **262**:81, 1926.

In 120 persons ranging in age from birth to 105 years, lipoid material stainable by sudan III was absent from the anterior segment of the mitral valve in only eight. The process begins in early childhood and was present in 52 of 153 children up to 6 months of age, this group including eighteen of the author's series and 114 children of another series. The material is deposited first just beneath the endocardium, occurring in the beginning within cells and then in the intercellular substance. With increasing age it is deposited also in the middle fibrous layer of the valve. The lipoid material is believed to be taken up directly from the blood stream, permeating the valve tissue with the nutritive fluids. The infiltration is usually not followed by degeneration, fibrosis or other reactive phenomena, the valve differing in this respect from the aorta.

O. T. SCHULTZ.

PECULIAR DEGENERATION OF SUPRARENALS IN ADDISON'S DISEASE. W. STEINBISS, Virchows Arch. f. path. Anat. **262**:286, 1926.

In a woman, aged 52, who died after the typical clinical syndrome of Addison's disease had been present for one year, the suprarenals were much decreased in size, their surface was nodular and a distinction between medulla and cortex was not apparent. Microscopically the medulla was decreased in

amount, but appeared normal in structure. Cortical cells were greatly reduced in number. Normal cells could not be seen. Those present had been transformed into large mononucleated and multinucleated spheroids, which were separated by loose connective tissue and lymphocytes. The cellular changes observed are interpreted as the result of a chronic degenerative process of unknown nature and origin.

O. T. SCHULTZ.

CHONDRODYSTROPHIA FETALIS. A. KAHLSTORF, Virchows Arch. f. path. Anat. **265**:84, 1927.

In eight chondrodystrophic fetuses, Kahlstorf found a smaller number of Hassall bodies in the thymus than in normal infants of the same ages, and eosinophilous cells were absent or greatly decreased in number. These changes are interpreted as evidence that chondrodystrophia is due to hypofunction of the thymus. The ingrowing periosteal streak, which separates the cartilage of the epiphysis from the diaphysis and results in failure of bone growth, is probably the result of persistence and hypertrophy of connective tissue which accompanies the vessels of the marrow canals of the cartilage.

O. T. SCHULTZ.

SARCOMA OF THE MAMMARY GLAND. W. THÜR, Virchows Arch. f. path. Anat. **265**:96, 1927.

A lymphosarcoma of the breast of a woman, aged 52, and a spindle cell sarcoma of the breast of a woman, aged 61, are described as examples of rarer forms of tumor of the mammary gland. The spindle cell sarcoma was associated with Schimmelbusch disease.

O. T. SCHULTZ.

MALIGNANT CALCIFIED EPITHELIOMA OF THE SKIN. N. GROMIKO, Virchows Arch. f. path. Anat. **265**:103, 1927.

In 1905, Malherbe described as calcifying epithelioma of the skin a tumor of variable size and slow growth, which is usually single, does not produce metastases, and does not recur after removal. Gromiko found eighty such calcifying epitheliomas recorded in the literature; recurrence was noted in only three of these. Gromiko adds a fourth case, in which the original tumor was situated on the upper third of the forearm, recurred twice and led finally to amputation of the arm.

O. T. SCHULTZ.

REACTION OF SUPRARENAL TO LOCAL INJURY. M. MANDELSTAMM, Virchows Arch. f. path. Anat. **265**:117, 1927.

The introduction of aspetic foreign bodies, glass or celloidin spicules, into the cortex of the suprarenal of the rabbit resulted in the disappearance of lipoid material from the damaged cells. Following this immediate reaction there occurred an increase in the lipoid content of the surrounding cortical cells.

O. T. SCHULTZ.

FATS AND LIPOIDS IN CERTAIN ENDOCRINE ORGANS. H. P. GROSSMANN, Virchows Arch. f. path. Anat. **265**:137, 1927.

Grossmann examined for their content in fats and lipoids the parathyroids, the thyroid and the suprarenal glands in 100 necropsies of persons varying in age from 4 weeks to more than 70 years. He defines fat as stroma cells filled with neutral fats, i. e., adipose tissue. Such tissue was present in all except six parathyroids, and in all but eleven thyroids. Adipose tissue cells occurred

singly or in small groups in the cortex of 21 of 150 suprarenals. Intracellular lipoids, chiefly phosphatids and lecithin, were uniformly present within the parenchyma cells of the three organs examined. The presence of fat is believed to depend on the nutritional state of the individual organ. The lipoid content of the suprarenal cortex is held to have no relationship to that of any other organ, but to be dependent on the lipoid content of the blood which reaches the cortex. The lipoids of the cells of the parathyroids and the thyroid are the result of intracellular metabolism, and their amount is an expression of the metabolic activity of the cells of these organs.

O. T. SCHULTZ.

ANOMALY OF CERVICAL VERTEBRAE. R. SIMON, Zentralbl. f. Chir. **54**:3247, 1927.

The cervical vertebrae, including the atlas, were fused in a solid mass (Klippel-Feil's disease).

CHANGES IN AMMON'S HORN IN APOPLECTIC CEREBRAL HEMORRHAGE. K. NEUBURGER, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:325, 1927.

In seventeen cases of cerebral hemorrhage, the author found changes in the subiculum which were probably secondary to vascular spasms. He believes that this is evidence that a generalized vasomotor disturbance is at the basis of the hemorrhage.

ROY GRINKER.

CULTURE STUDIES OF LEUKEMIC BLOOD. HANS HIRSCHFELD, Folia haemat. **34**:39, 1927.

Tissue cultures in vitro are widely used in experimental pathology. Carrel and Ebeling were able, moreover, to isolate pure cultures of monocytes from normal blood and to demonstrate their transformation into fibroblasts. M. R. and W. H. Lewis cultivated blood in a hanging drop. In the blood of a frog's heart, they observed the formation of monocytes, and in the blood of other animals they noticed the transformation of leukocytes into macrophages. Maximo cultivated in vitro leukocytes of rabbit's blood in which he was able to follow up the transformation of monocytes into macrophages (polyblasts, clasmotocytes). Awrorow and Timofejewsky were first to study in vitro the blood leukocytes from leukemic patients. Hirschfeld cultured the leukocyte from patients with chronic lymphatic leukemia, chronic myelogenous leukemia and acute myelogenous leukemia. He noticed that in the cultures only the monocytes became transformed into fibroblasts. In cases of acute myelogenous leukemia, the myeloblasts undergo transformation, and in the chronic forms the myeloblasts and the myelocytes change into other varieties of cells. The myelocytes and the myeloblasts are likewise endowed with the potentiality to form syncytial cellular agglomerations and fibroblast-like cells.

B. M. FRIED.

THE MYELOBLAST—ITS OCCURRENCE UNDER NORMAL AND PATHOLOGIC CONDITIONS, AND ITS RELATIONS TO LYMPHOCYTES AND OTHER BLOOD CELLS. H. DOWNEY, Folia haemat. **34**:65, 1927.

The article by Downey is practically a monograph on the myeloblast. The author goes into great details concerning the genesis and the potentialities of this cell. The discussion is comprehensive and scholarly. The article is accompanied by an extensive bibliography and by numerous colored pictures.

B. M. FRIED.

THE IDENTIFICATION OF MYELOBLASTS WITH VITAL STAINS. M. E. SIMPSON and J. M. DEMING, Folia haemat. **34**:103, 1927.

Stimson and Deming investigated the blood of patients with acute myelogenous leukemia by the use of the supravital stain technic. They arrive at the conclusion that this method of blood staining furnishes "a valuable addition to available methods for recognition of the youngest myeloid cells."

B. M. FRIED.

TWO CASES OF PAPILLOMA OF THE RENAL PELVIS. S. SHIMOMURA and S. KANISAWA, Acta Dermatologica (Japanese) **10**:203, 1927.

One case occurred in the pelvis of the left kidney in a man, aged 54; the other case occurred in the pelvis of the right kidney in a patient, aged 40, and in this case the papillomatous growth involved the upper part of the ureter.

Pathologic Chemistry

BLOOD: SPECIES REACTION. E. O. MANOILOFF, Am. J. Phys. Anthrop. **10**:323, 1927.

On ground of our tests, we find it necessary to emphasize the following:

1. The species reaction on our material has given the possibility of distinguishing cattle from horses by their blood serums in 100 per cent of the cases.

2. This reaction is not biologic, but purely chemical, as it gives a correct answer with both fresh and old serums.

3. Considering that we obtain a correct answer also with coagulated serum, we may come to the important conclusion that the X of species does not belong to enzymes and to ferments in general.

4. The X of the species lies in the serum itself, i. e., the species difference lies evidently in a special albumin body. Every species apparently has its own specific albumin complex, and it is very probable that every human race as well as animals will be found to have its own albumin complex also.

AUTHOR'S SUMMARY.

A STUDY OF THE INORGANIC CONSTITUENTS OF THE SERUM IN CHILDREN WITH ACUTE NEPHRITIS. KENNETH D. BLACKFAN and BENGT HAMILTON, Bull. Johns Hopkins Hosp. **41**:322, 1927.

In cases of acute glomerular and tubular nephritis in children, the total fixed base of the serum has been determined, and an attempt has been made to obtain an estimate of the amount of total electrolytes in the serum. In tubular nephritis, the total fixed base is nearly always markedly decreased, and the same is probably true as to the total electrolytes. In glomerular nephritis, there often is a tendency to changes of the same kind as in tubular nephritis, although not so marked as in the latter condition. In one patient with very severe symptoms, however, the base was increased, probably also the total electrolytes. Possibly this observation may be explained as a retention of electrolytes due to impaired kidney function.

AUTHORS' SUMMARY.

THE ACID-BASE COMPOSITION OF URINE FROM AN EPILEPTIC CHILD. JAMES L. GAMBLE and BENGT HAMILTON, Bull. Johns Hopkins Hosp. **41**:389, 1927.

The acid-base composition of urine was determined in a series of twenty-four hour specimens from an epileptic child. An accurate constancy of dietary

factors and of fluid intake was maintained. It was found that during periods of seizures a greatly increased excretion of total acid and of total fixed base occurred. The increment of total acid was chiefly composed of chloride ion, while the approximately corresponding extension of fixed base was nearly entirely sodium. The factors regulating the excretion of fixed base, viz., urine acidity and ammonia, remained nearly stationary. These observations are taken as indicating a loss of extracellular body fluid in the urine during the periods of active epilepsy. Agreeing with this interpretation, corresponding increments of urine volume were found.

AUTHORS' SUMMARY.

THE ORGANIC PHOSPHORUS OF THE CEREBROSPINAL FLUID. GUY E. YOUNGBURG, J. Lab. & Clin. Med. **12**:845, 1927.

The cerebrospinal fluid of 200 patients from hospital and outpatient departments has been analyzed, particularly as to content of organically bound phosphorus. Between 0.06 and 0.59 mg. per cent of phosphorus was found, the great majority being between 0.1 and 0.3 mg. per cent. This phosphorus is not in the form of lipoids, but in all probability in protein combination. No diagnostic value can yet be attached to the determination of organic phosphorus. Organic and inorganic phosphorus contents are independent of each other.

AUTHOR'S SUMMARY.

THE XANTHOPROTEIC REACTION AND FREE AND CONJUGATED PHENOLS IN THE BLOOD AND SPINAL FLUID OF PATIENTS WITH UREMIA. CARLO CIPRIANI and ANGELO FERRERO, Arch. per le sc. med. **49**:257, 1927.

The xanthoproteic reaction of the blood filtrate is increased in true uremia and can be introduced in practical medicine for its simplicity and small quantity of material necessary. It does not always appear to be of great diagnostic value as a measure of retention of nitrogen.

The experimental evidence shows that, in the more advanced stages, the substances causing an augmentation in the xanthoproteic reaction are free phenols and paracresols. Normally, these substances are detoxified by being paired off with sulphuric and glycuronic acids, but in uremia the normal mechanism is disturbed causing these compounds to circulate free. The xanthoproteic reaction on a protein-free spinal fluid is either negative or slightly positive, even though the corresponding blood filtrate is strongly positive. A slight positive reaction appears only during the last stages of the disease which runs parallel with traces of free phenols and causes one to admit that uremia is due to the inability of the organism to detoxify these compounds. Many examples of clinical cases are given.

A. J. SALLE.

THE DEXTROSE CONTENT OF THE RED BLOOD CELLS OF MAN IN NORMAL AND PATHOLOGIC CONDITIONS. ANGELO VIGNOLO PALOMBELLA, Arch. per le sc. med. **49**:678, 1927.

The dextrose content of the red blood cells in normal subjects varied between 0.05 and 0.07 per cent. In all hyperglycemic patients examined, exclusive of diabetic patients, this value remained around the normal, while in the patients with diabetes there was always an increase. This increase ran parallel with the gravity of the disease. It is concluded that the red cells of man in physiologic condition are permeable to dextrose and that the increase in permeability in the diabetic patient is an index of the diminished regulatory action of the cellular membrane in relation to the state of gravity of the disease.

A. J. SALLE.

CHEMICAL ANALYSIS OF THE SPLEEN IN LIPOID CELL SPLENOHEPATOMEGALY (NIEMANN-PICK). B. BRAHN and L. PICK, Klin. Wchnschr. **6**:2367, 1927.

The spleen weighed 198 Gm. and chemically it contained per 100 grams moist weight, 15.1 total lipin, 1.39 cholesterol, 0.4 cholesterol ester, and 10.3 lecithin. These results agree with other reports in the belief that the metabolic disturbance concerns the phosphatids. There is also relatively as great an increase of the cholesterol, and apparently also of the cholesterol esters.

E. F. HIRSCH.

THE CONTENT OF A PANCREATIC CYST. W. DEUTSCH and H. GRUBEL, Klin. Wchnschr. **6**:2369, 1927.

The presence of pancreatic lipase and amylase, and the absence of activated trypsin were demonstrated.

E. F. HIRSCH.

INTRACELLULAR HYDROGEN ION CONCENTRATIONS. I. METHODS. M. SCHMIDTMANN, Ztschr. f. d. ges. exper. Med. **57**:123, 1927.

This paper is a critique of the various methods hitherto employed to determine the intracellular hydrogen ion concentration. (Schmidtmann refers to his previous paper in Ztschr. f. d. ges. exper. Med. **45**:714, 1925. In order to make the present abstract clear, some of the statements contained in the earlier paper are given here.) The author discusses first the earliest method, used by Michaelis, which consists in expressing the cellular and tissue juices from an organ, and measuring the p_H of such fluid either electrometrically or colorimetrically. The reaction of such fluids is always near the neutral point, muscle juice alone being slightly acid. Later, vital staining of the entire animal was resorted to; this technic was largely used by Rous at the Rockefeller Institute. With the development of the microdissection technic, it became possible either to inject an indicator solution into individual cells or to introduce a minute granule of the indicator in dry form. The latter method was employed by Schmidtmann. He used the Peterfi microdissection apparatus, and injected with glass needles a minute particle of the dry indicator into isolated cells, or into cell complexes — usually frozen sections of fresh unfixed material, or fresh scrapings. The indicators used belonged to the usual Clark's series: methyl red, phenol red, brom cresol purple, brom thymol blue. A granule of such an indicator injected into a cell would be dissolved by the intracellular fluid, and stain the interior of the cell. The color produced was compared with standards made by placing minute particles of the indicator into buffer solutions of known p_H value. Schmidtmann emphasizes that the p_H values obtained have only relative and not absolute value. He next discusses the effect of injury which necessarily is produced when the indicator is introduced. If an organ is vitally stained by perfusing it with Ringer's solution containing the indicator, and a cell is now injured by puncturing it with a microdissection needle, the color of the cell contents shifts at once to its more acid range; mechanical trauma alone therefore changes the intracellular reaction in the direction of increased acidity. But this shift is only a momentary one, for within a few seconds the color returns to its previous shape, hence, no lasting change in reaction occurs.

In normal living cells injection of the indicator causes staining of the cytoplasm, but the nucleus remains unstained. In dying or dead cells the protoplasm becomes more granular, its reaction more acid (a decrease in p_H of from 0.3 to 0.4) and the nucleus stains. The intracellular acidity progresses until a certain maximum is reached, after which further changes do not occur.

If the indicator is injected into one of a group of cells the normal connections of which are intact (say into one of a group of epidermal cells), the dye spreads from the injected into the neighboring noninjected cells—the nuclei remaining unstained. The intracellular reaction varies in different kinds of cells, and in most cells is slightly acid, about p_H 5.8 to 6.9. For example the islet cells of the pancreas are more acid than the neighboring acinar cells; the cells of the basal layer of the epiderm have slightly alkaline reaction, while the more superficial cells have a lower p_H. The egg cells of the ovary differ from all other cells in that they have distinctly alkaline reaction, about p_H 7.8.

BALDUIN LUCKE.

INTRACELLULAR HYDROGEN ION CONCENTRATION. II. REACTION AND PERMEABILITY OF INFLAMMATORY AND NEOPLASTIC TISSUES. M. SCHMIDTMANN and K. MATTHES, Ztschr. f. d. ges. exper. Med. **57**:127, 1927.

Cells from fresh human tumor material examined within twenty minutes after surgical removal behave differently from cells of the adjacent normal, i. e., nonneoplastic tissue. The indicator diffuses more rapidly through the cytoplasm, the nuclei stain at once and the reaction of the nuclei and the cytoplasm is different from that of the surrounding tissue cells. For example, in a case of adenocarcinoma of the stomach, the fresh, unstained cells scraped from the tumor and from the adjacent normal gastric mucosa did not show any morphologic difference microscopically. On injection of brom cresol purple the nuclei of the normal mucosal cells remained unstained, their cytoplasm became bluish violet. In the tumor cells the nuclei stained an intense purple, the cytoplasm greenish yellow.

Granules of various indicators were injected into frozen sections of unfixed fresh cancerous and adjacent normal tissue. In the tumor cells the dyes dissolved rapidly, and the nuclei of the cells stained deeply. The p_H of the cytoplasm of the tumor cells was from 6.3 to 6.2; the p_H of the nuclei, 6.5. In the noncancerous tissue the dye granules dissolved slowly; there was no nuclear staining, the p_H of the cytoplasm was from 6.9 to 6.7.

It is known that in dead cells the nuclei stain. Is it possible that the tumor cells were dead? This question was answered by suspending both tumor cells and normal tissue cells in Ringer solution having a p_H range from 5.4 to 8.2. Neither the tumor cells nor the normal tissue cells took up the dye. In dead cells, on the other hand, the protoplasm soon takes on the reaction of the medium.

In tumor material obtained from autopsies the reactions were the same during the first hour after death as described for surgical material. Three hours after death the difference between tumor cells and normal tissue cells was less distinct; after six hours differences were not apparent.

In brief, the cytoplasm of tumor cells is more acid than the cytoplasm of normal tissue cells; in living tumor cells the nuclei are stained by indicators; this does not occur in living tissue cells.

All cellular malignant tumors, cancers and sarcomas, behaved in the manner described. No cellular benign tumors were studied. In slowly growing, poorly cellular, scirrhous cancers the reactions mentioned did not occur.

The authors examined exudative and regenerating cells, such as leukocytes, fibroblasts from granulation tissue, and regenerating muscle cells, and none of these cells had the characteristic reactions of neoplastic cells. On the other hand, cells from experimental cancers of animals behaved like human cancer or sarcoma cells. It is concluded that the nuclear membrane of cellular malignant tumors is permeable to indicators, and that the intracellular reaction is more acid. There appear to be profound differences in the physicochemical constitution between neoplastic and normal tissue cells.

BALDUIN LUCKE.

Microbiology and Parasitology

HOST-PARASITE RELATIONS BETWEEN IODAMOEBA WILLIAMSI AND CERTAIN MAMMALIAN HOSTS. SEPTIMA C. SMITH, Am. J. Hyg. **8**:1, 1928.

Excystation in the rat occurs in the jejunum between one and three hours after inoculation.

THE SIGNIFICATION OF THE AGE DISTRIBUTION OF POLIOMYELITIS. W. LLOYD AYCOCK, Am. J. Hyg. **8**:35, 1928.

In Vermont more cases of poliomyelitis occurred in the younger age groups in urban than in rural communities. The age distribution of measles, diphtheria and poliomyelitis is of the same order, and the incidence of each disease in the various age groups is proportional to the concentration of the population. This fact indicates that the mechanism involved is similar for all these diseases. In poliomyelitis immunity, largely subclinical, is responsible for the age distribution. It appears that the virus of the disease is just as widely distributed as those of measles and diphtheria, and in the course of this distribution the majority of persons become immunized.

THE COEXISTENCE OF SYPHILIS AND PULMONARY TUBERCULOSIS: IN 659 CASES WITH 125 AUTOPSIES. CHARLES C. HABLISTON and W. OLIVER MCLANE, Am. Rev. Tuberc. **16**:100, 1927.

The coexistence of syphilis and pulmonary tuberculosis ocurred in 14.2 per cent of the patients treated in the tuberculosis department of the city hospital in Baltimore. Syphilis, as a latent condition, has shown little effect on the course of pulmonary tuberculosis, the results obtained being comparable to those in nonsyphilitic tuberculosis patients. Syphilis, as an active disease, showed a decidedly unfavorable influence on the course of pulmonary tuberculosis, the death rate being higher than in any other class of patients treated in the hospital. Beneficial effects of treatment with arsenicals were secured without untoward effect on the tuberculous disease. By their use in cases of pulmonary tuberculosis associated with active syphilis a decline of 14.5 per cent in the mortality and an increase of 9.8 per cent in improvement was noted.

H. J. CORPER.

A CASE OF A PRIMARY COMPLEX IN AN ADULT WITH FOCAL TUBERCULIN REACTION IN THE TRACHEOBRONCHIAL LYMPH NODES. ISRAEL RAPPAPORT and RICHARD T. ELLISON, Am. Rev. Tuberc. **16**:256, 1927.

A case is reported with marked focal reaction in the tracheobronchial lymph nodes of an adult, following a Pirquet test, demonstrated by roentgen-ray examination. Two possible explanations of the clinical and roentgen-ray pictures are offered, neither of which is considered entirely satisfactory. It may have been an exacerbation of an old primary complex, but this would necessitate a reversal of the immunobiologic state to a condition of allergy characteristic of primary infection. It may be the reappearance of a primary complex in a man, aged 30, taking the form of an acute bacillary infection and producing an immunobiologic state characteristic of childhood, but this necessitates the assumption that the allergy of practically certain early childhood contact infection had been entirely lost. Tubercle bacilli were found in the expectorated material in the absence of pulmonary tuberculosis.

H. J. CORPER.

THE ISOLATION OF TUBERCLE BACILLI FROM CONTAMINATED TUBERCULOSIS MATERIALS. H. J. CORPER and NAO UYEI, Am. Rev. Tuberc. **16**:299, 1927.

Crystal violet can replace the prewar gentian violet in egg mediums and in about the same concentration to inhibit the development of contaminators during the primary isolation of tubercle bacilli from contaminated sources. Of a large number of reagents tested (urea, sodium carbonate, ammonium hydroxide, ammonium carbonate, sodium hydroxide, and sulphuric or hydrochloric acids) to destroy the rapilly growing micro-organisms in contaminated materials for isolating tubercle bacilli, sulphuric acid was found most serviceable. Hydrochloric acid and sodium hydroxide also proved satisfactory, while urea, sodium carbonate, ammonium hydroxide and ammonium carbonate proved entirely unsatisfactory. In quantitative seeding tests potato medium was found superior to Dorset's egg medium, Petroff's gentian violet-egg medium, glycerin-agar, and Long's nonprotein medium, in favoring the growth of tubercle bacilli when present in small numbers. Crystal violet-potato medium, in which the potato cylinders were treated with 0.003 per cent crystal violet solution, proved suitable for the isolation of small numbers of tubercle bacilli in sputum. This medium proved superior to Petroff's gentian violet-egg medium. A new method for the isolation of tubercle bacilli from contaminated sources is proposed, using 6 per cent sulphuric acid at 37 C. for thirty minutes in the preliminary treatment of the tuberculous material, and crystal violet-potato medium for culturing the bacilli.

H. J. CORPER.

AN INVESTIGATION OF FILTRABLE FORMS OF THE TUBERCLE BACILLUS AND OF PROTECTIVE SUBSTANCES IN THE FILTRATES: EXPERIMENTS WITH FILTRATES OF TUBERCULOUS SPUTUM. CLEVELAND FLOYD and MARGARET CHASE HERRICK, Am. Rev. Tuberc. **16**:323, 1927.

In a limited series of filtration tests of tuberculous sputum, positive results were obtained in two animals inoculated with one specimen, and suggestive forms were obtained in two other instances. The autopsy observations in all these guinea-pigs agree with the published reports in showing no typical tuberculous picture, the only pathologic effects noted being confined to the lymph nodes, particularly the tracheobronchial lymph nodes. Protective substances were not noted in the filtrate from positive sputums, not only when the laboratory culture was used but also when filtrate and homologous culture were inoculated. This is in contrast to the work of Boquet, Negre and Valtis. All cultures of filtrates were uniformly negative.

H. J. CORPER.

A STUDY OF THE BACTERIAL ETIOLOGY OF TUBERCULOSIS: EXPERIMENTS WITH NON-ACID-FAST MICROORGANISMS FROM TUBERCULOUS SPUTUM. FRANCIS M. DUFFY, Am. Rev. Tuberc. **16**:330, 1927.

A study was made of two groups of micro-organisms, one a sporeformer similar to *Bacillus subtilis*, and the other a group composed of coccoid bodies, diphtheroid bacilli and granular forms. These forms possess pathogenic powers. Their relationship was indicated by three methods of study: (1) by pathogenicity, (2) by anaphylactic reactions, and (3) by precipitin tests on tuberculous serum. They also possess a protein relationship to the bacillus of Koch. The bacillus of Koch is apparently the end-micro-organism of a chain of mutation forms.

H. J. CORPER.

THE RELATION OF GLYCEROL IN CULTURE MEDIA TO THE GROWTH AND CHEMICAL COMPOSITION OF TURERCLE BACILLI. ESMOND R. LONG and LUCY L. FINNER, Am. Rev. Tuberc. **16**:523, 1927.

As the concentration of glycerin in the synthetic medium (Long's) rises from 0.5 to 12.5 per cent, the growth range, the yield of dry bacilli increases tenfold, and the proportion of the dry weight as lipidin is multiplied two and a half times. In as much as approximately two thirds of this increasing lipin is wax, glycerin may be looked on as a progenitor of the waxy constituents of the bacillus. Growth at high concentrations of glycerin is associated with increased intensity of acid-fastness. At 5 per cent glycerin, the concentration used routinely in laboratory mediums, the proportion of the dry weight of the bacilli as lipin is only slightly greater than when the glycerin concentration is 0.5 per cent, although growth is far more luxuriant when the larger amount of glycerin is present. It is only at the higher concentrations of glycerin that the lipin content of the bacilli is much changed. The importance of glycerin in laboratory cultures, and the inefficiency of other combinations of carbon in promoting laboratory growth, indicate the probable importance of variations in glycerin in animal tissues in resistance to tuberculosis.

H. J. CORPER.

VACCINIFORM BLEPHARITIS DUE TO HERPES VIRUS. H. B. ANDERVONT and J. S. FRIEDENWALD, Bull. Johns Hopkins Hosp. **42**:1, 1928.

From a vesicular and pustular eruption on the eyelids of a girl, aged 14 years, a virus was obtained that in rabbits caused symptoms and lesions similar to those caused by the herpes virus.

FILTRABLE VIRUSES: A CRITICAL REVIEW. T. M. RIVERS, J. Bact. **14**:217, 1927.

In the majority of virus diseases, a close relationship between the etiologic agents and the cells of the hosts exists. This intimate type of parasitism is emphasized by the fact that some of the diseases exhibit a striking species specificity, that the viruses have resisted cultivation in the absence of living cells, that characteristic or specific pathologic changes are frequently observed in cells affected by viruses, and, finally, that a host once recovered from a virus disease usually exhibits a lasting immunity.

AUTHOR'S SUMMARY.

LIGHT ACTIVATED HEMOLYSIN PRODUCED BY B. INFLUENZAE. HUGH K. WARD, J. Bact. **15**:51, 1928.

Grown on fresh horse blood agar containing hematin *B influenzae* does not produce hemolysis around the colonies when incubated in the dark, but when the plates are exposed to daylight or artificial light an area of clear hemolysis appears around the colony.

ACTION OF B. DIPHTHERIAS AND RELATED ORGANISMS ON GLUCOSAMINE. WILLIS C. NOBLE JR. and FLORENCE E. D. KNIGHT, J. Bact. **15**:55, 1928.

There was no correlation between ability to ferment glucosamine and to produce diphtheria toxin.

ON THE TITRATION OF BACTERIOPHAGE AND THE PARTICULATE HYPOTHESIS. H. CLARK, J. General Physiol. **11**:71, 1927.

The theory of the serial dilution method is worked out mathematically on the basis of the simple particulate hypothesis of bacteriophage, and it is found

that with a dilution constant of 0.1, only about 60 per cent of parallel runs of the same solution should yield the same end-point, the average being determined by a great number of titrations of each of numerous solutions. The actual percentage as estimated by Dr. Bronfenbrenner is 85. The writer has no explanation to offer of this discrepancy.

H. E. Eggers.

The Reaction of the Dog to the Continuous Intravenous Injection of B. Coli. William F. Peterson, Ernst F. Müller and William Boikan, J. Infect. Dis. **41**:405, 1927.

The clinical reaction of dogs to the continuous injection of *B. coli* has been studied and correlated with simultaneous lymph analysis. The reaction can be divided into five periods: the latent period; the period of splanchnic stimulation; the period of fluctuations, with cellular efforts of restoration of the equilibrium; the period of maximum injury, and the premortal period. Only during the period of maximum injury do bacteria pass from the blood stream to the lymph channels. In certain animals (differing chemically from the normal) the preliminary reaction may be reversed (paradoxic reactions).

Authors' Summary.

Streptococci as a Cause of Spontaneous Abortion. Allan F. Reith, J. Infect. Dis. **41**:423, 1927.

Pleomorphic, anaerobic, green-producing or faintly hemolytic streptococci from the tonsils and placenta of a woman who had had repeated spontaneous abortions produced abortion in four pregnant rabbits and hemorrhage in the uterus in eight out of ten nonpregnant rabbits after intravenous injection. In thirteen rabbits given injections with a throat culture from the same woman ten months after tonsillectomy, and with tonsil and prostate cultures from her husband, no lesion in the uterus were seen. These results corroborate the theory that foci of infection may harbor streptococci which possess properties that may give rise to spontaneous abortion.

Author's Summary.

Action of Hemotoxins on Oxygenated and Reduced Blood. Guilford B. Reed, J. H. Orr and W. A. Campbell, J. Infect. Dis. **41**:434, 1927.

In agreement with earlier work of Neill it was found that the oxidation of *B. welchii* toxin by exposure of toxic filtrates to the air for twenty-four hours results in considerable loss of hemotoxic action.

The hemolysis of oxygenated red cell suspensions requires a much higher concentration of *B. welchii* toxin than reduced red cell emulsions. It is suggested that this may result from an oxidation, reduction relationship between the toxin and hemoglobin or that it may depend on a difference in the absorption of toxin by oxygenated and reduced blood.

Authors' Summary.

An Epidemic of Hemorrhagic Septicemia in Guinea-Pigs. Guilford B. Reed and G. H. Ettinger, J. Infect. Dis. **41**:439, 1927.

An epidemic is described involving the death of 60 per cent of a colony of guinea-pigs. An organism resembling *Pasteurella cuniculicida* was isolated from animals in the epidemic, which when injected into unexposed guinea-pigs reproduced the disease.

Authors' Summary.

EFFECT OF CL. SPOROGENES ON TOXIN PRODUCTION BY CL. BOTULINUM. E. WAGNER SOMMER and KATHRYN GLUNZ, J. Infect. Dis. **41**:442, 1927.

Spore suspensions of *Cl. botulinum* and *Cl. sporogenes* inoculated in varying relative amounts into meat, spinach and asparagus mediums which are incubated for ten days and tested for the presence of toxin, reveal botulinum toxin in all the meat cultures in which *Cl. botulinum* is present irrespective of the number of sporogenes. The inoculation of an equal or greater number of *Cl. botulinum* with sporogenes is usually necessary for toxin production in spinach. In asparagus, a poorer toxin medium, a more deleterious influence of sporogenes on botulinum toxin has been noted. In meat, spinach and asparagus mediums increasing numbers of sporogenes gradually diminish the strength of the toxin.

AUTHORS' SUMMARY.

THE PRODUCTION OF LOCAL RENAL LESIONS IN RABBITS BY INTRAVENOUS INJECTIONS OF CERTAIN STRAINS OF B. COLI. HENRY F. HELMHOLZ, J. Infect. Dis. **41**:448, 1927.

In studying various strains of colon bacilli isolated from the urine of patients with pyelitis, from the urine of rabbits and from the gastro-intestinal canal of rabbits, three strains showed a specific tendency to produce local renal lesions. More than two thirds of the animals given injections with these strains showed renal localization without corresponding increase in localization elsewhere. This is the first report of the specific localization of the colon bacillus.

AUTHOR'S SUMMARY.

ON THE BIOLOGY OF B. FUSIFORMIS. JOSEPHINE S. PRATT, J. Infect. Dis. **41**:461, 1927.

Fusiform bacilli seem to be present normally in small numbers in the throat; being found in 100 per cent of the human beings examined, in 100 per cent of the monkeys, in 66 per cent of the guinea-pigs and in 48 per cent of the rabbits in this series. Under certain abnormal conditions these bacteria increase and probably function as secondary infecting agents. On the basis of sucrose fermentation two cultural groups are demonstrable, but the difference bears no relationship to the source of the cultures. Complement fixation failed to prove the existence of serologic groups, each antigen fixing its homologous antiserum only, indicating a serologic heterogenicity. The fusiform bacillus and the spirochete commonly found together are different micro-organisms.

AUTHOR'S SUMMARY.

RELATIONSHIP OF M. MELITENSIS AND BR. ABORTUS. C. CERRUTI, J. Trop. med. **30**:230, 1927.

To avoid the confusion arising from the name "melitensis," in view of its pathogenicity to man, producing, as it does, undulant fever, and in the case of animals, abortion, often epizootic in character, Cerruti suggests that it be given the name of *Brucella melitensis-abortus*, Bruce, 1887.

MICROSCOPIC CHANGES OF TULAREMIA IN THE TICK DERMACENTOR ANDERSONI AND THE BEDBUG CIMEX LECTULARIUS. EDWARD FRANCIS, Pub. Health Rep. **42**:2763, 1927.

Ticks play a most important rôle in the transmission of tularemia from rabbit to man and from rabbit to rabbit, and in the permanent maintenance of the infection in nature. The additional observations that ticks, infected in the

laboratory, remained infected for 247 days and that ticks hereditarily transmitted the infection through their eggs to the next generation of ticks, led to a study of the microscopic changes in artificially infected ticks. The result was a demonstration, by serial sections or by culture, that *Dermacentor andersoni* is a true biologic host of *Bacterium tularense* that it harbors the organism not only in its feces but also in the epithelial cells of its digestive tract and malpighian tubes, and in its colonic fluid. Evidence of infection was not seen in sections of the salivary glands, ovaries, male genitalia, heart, brain or muscles. This led to the belief that transmission by ticks is due to the mechanical entrance of infected feces through the biting wound.

Bedbugs have not been shown to play any part in nature, either in the transmission of tularemia to the man or among animals. But, under experimental conditions, they have been found to harbor the infection in their feces for 250 days and to be feeble transmitters of the disease to white mice, by biting.

By serial sections, *Bacterium tularense* was demonstrated in infected bugs in fresh blood contents of the anterior portion of the midgut, in the epithelial cells, especially of the posterior portion of the midgut, and occasionally in the epithelium of the malpighian tubes but not in the esophagus, salivary apparatus, reproductive organs, brain or muscles. By cultures, the organism was recovered from the colonic fluid. By injection into guinea-pigs, the feces were always found infective. From all data at hand the view has gained that transmission by bedbugs by biting was probably due to the mechanical entrance of infected feces through the biting wound.

AUTHOR'S SUMMARY.

BACTERIAL PROTEINS: THE PRESENCE OF ALCOHOL-SOLUBLE PROTEINS IN BACTERIA. K. GOADBY, Proc. Roy. Soc. **102B**:137, 1927.

"By a method which is shown to produce a minimum change in the protein constituents, an alcohol-soluble protein, having many of the characters of the alcohol-soluble proteins of the seeds of cereals, has been extracted from streptococci, staphylococci, *Bacillus hoffmann, B. typhosus, B. coli communis, B. paracoloides,* and *Micrococcus catarrhalis.* The Molisch-reacting substance appears to form an important constituent of bacterial structure."

AUTHOR'S SUMMARY.

A COMPARISON OF THREE DIFFERENT SYSTEMS OF CLASSIFICATIONS OF DYSENTERY BACILLI: ENGLISH, GERMAN AND JAPANESE. DIMITRIJE KALIC, J. Path. & Bact. **30**:593, 1927.

Having compared three different serologic classifications of dysentery bacilli, I find that Vz type Andrewes corresponds to Kruse's A group; Andrewes' X type to Aoki's type II; Andrewes' Y (original Hiss-Russell) to Kruse's D and Aoki's Type I; Andrewes' Z to Kruse's H and Aoki's X.

PRELIMINARY NOTE ON A NEW PATHOGENIC SPIROCHAETE. C. NICOLLE, C. ANDERSON and J. COLAS-BELCOUR, Arch. Inst. Pasteur de Tunis **16**:219, 1927.

A new spirochete, *Sp. normandi,* of which the agent of transmission is the *Ornithodorus normandi,* the ordinary reservoir of the virus being a bird, is described.

M. S. MARSHALL.

STUDIES ON TYPHUS FEVER. P. HAUDUROY, Arch. Inst. Pasteur de Tunis **16**: 261, 1927.

The quasispecific anti-Proteus X19 bacteriophage is capable of bringing about the production of filtrable forms of this organism. Such bacteriophage material

free from filtrable forms, does not produce disease or immunity in guinea-pigs. Bacteriophage was not found in patients in the course of infection.

M. S. MARSHALL.

INTRACELLULAR INCLUSIONS OF CONJUNCTIVAL EPITHELIUM. C. TRAPEZONTZEWA, Arch. Inst. Pasteur de Tunis **16**:271, 1927.

The author's observations were made primarily in trachoma. The study embraces the results of experimental work, and includes a color plate of nine figures. Views of the origin and nature of the inclusions are expressed.

M. S. MARSHALL.

NATURAL GRANULAR CONJUNCTIVITIS OF RABBITS. C. NICOLLE and U. LUMBROSO, Arch. Inst. Pasteur de Tunis **16**:286, 1927.

The filtrable virus of natural granular conjunctivitis in the rabbit is transferable to man, but differs from the typical natural or experimental infection in man, in its longer period of incubation, and in its primary localization in the lower surface.

M. S. MARSHALL.

NEGATIVE ATTEMPTS TO REPRODUCE SYPHILIS IN THE DOMESTIC CAMEL. C. NICOLLE and E. BURNET, Arch. Inst. Pasteur de Tunis **16**:300, 1927.

NATURE OF THE TUBERCULOUS INFLAMMATORY PROCESS. H. KALBFLEISCH, Beitr. z. path. Anat. u. z. allg. Path. **78**:187, 1927.

In an article of thirty-eight pages with only seven references, Kalbfleisch details the results of a study of the tissue reactions which occur in the mesentery, conjunctiva and cutis of the rabbit following injection of small doses of tubercle bacilli. The entire series of phenomena which follow such an injection and which result in the tuberculous inflammatory reaction, he ascribes to a primary and early action on the neurovascular mechanism of the injected tissue, he being in this respect a strict adherent of Ricker in the importance which the latter attaches to the rôle of this mechanism in inflammation. The later changes which occur in the fixed tissues and the final necrosis are not the result of a reaction to the tubercle bacillus itself or to its products, but are the outcome of the stimulative and irritative effects on terminal blood vessels. Secondary vascular stimuli, due to these earlier tissue reactions and not to the bacilli, maintain the process.

O. T. SCHULTZ.

THE PROBLEM OF THE CAVITY FROM THE PATHOLOGIC AND ANATOMIC VIEWPOINT. A. SCHMINCKE, Beitr. z. Klin. d. Tuberk. **67**:124, 1927.

The structure of cavities is dependent on the immune-biologic state in which they develop. They are accordingly classified in regard to Ranke's three stages. The two processes directly responsible for the formation of cavities are the (usually acute) sequestration in a larger caseous area, and the pyogenous process in which liquefaction is a dominant factor. The primary cavity develops from the primary parenchymatous focus; it is, therefore, characterized by its subpleural location and caseation of the regional lymph glands. This type of cavity may be sharply outlined, with a relatively clean wall, or it may be partially encapsulated and showing, at the same time active progression, or it may be a sequestration cavity in a pneumonic area. This last type resembles the secondary cavities;

the latter are frequently multiple and may be found anywhere in the lung. Their progression, due to the hypersensitiveness of the tissue and their lack of resistance, is rapid, leading to large and irregular formations. Their walls may show a process of cleaning, leaving a corrugated inner surface. The cavity which is characteristic for the late secondary stage, is round, thin walled, often isolated, its inner surface shows a rather smooth membrane. The tertiary cavity contains always more or less new formed fibrous tissue and its wall and characteristic tuberculous granulation tissue. These two tissue elements with the innermost necrotic layer produce the typical three-layered wall of the tertiary cavity. The growth, the potential dangers, and the possible healing of cavities are further discussed.

MAX PINNER.

THE VIRUS OF MEASLES. R. DEGKWITZ, Klin. Wchnschr. **6**:2364, 1927.

The virus of measles can be kept alive in vitro, if blood from a patient taken at the onset of the eruption, is added to a physiologic sodium chloride solution of the same anion, kation and *p*H concentration as the blood, in the proportion of 1:7 to 1:10 and kept at 0 C. Experimental infections can be produced with material that bacteriologically is sterile. Sterile filtrates of nasal secretions obtained in the prodromal stages of the disease, diluted and passed through a Berkfeld filter have the same effect. The virus can be grown in the incubator on culture mediums consisting of plasma from susceptible people diluted with the described saline solution in the proportion of 1:6 to 1:7. To keep the virus alive and make it grow, living cells must be added or a small number of symbiotic slow growing bacteria. With sterile filtrates of such inoculated cultures reactions like measles can be produced in susceptible people, and specificity is demonstrated in that these persons become immune against large doses of the original infectious material. Monkeys (*Macacus rhesus)* are susceptible and the specificity of the disease is manifested in that their convalescent serum protects human beings, while normal serum fails.

AUTHOR'S SUMMARY.

DUODENAL ASPIRATIONS FOR TYPHOID BACILLI IN TYPHOID FEVER. N. HENNING and A. LECHNER, München. med. Wchnschr. **74**:579, 1927.

Typhoid cultures were made from the duodenal contents and the bile, aspirated from thirty-six patients with typhoid, with positive results in 26 per cent of the former and 53 per cent of the latter materials.

J. D. WILLEMS.

TETANUS FOLLOWING SAND FLEA BITES. W. ROHARDT, München. med. Wchnschr. **74**:1054, 1927.

Four instances of tetanus following the stinging by sand fleas are reported.

J. D. WILLEMS.

AN ABSCESS FOLLOWING TYPHOID MASTITIS. W. GERLACH, München. med. Wchnschr. **74**:1324, 1927.

An adult woman developed mastitis during convalescense from typhoid fever. A small hard nodule remained in the breast. Several years later this enlarged, became painful and inflamed, and on incision yielded a thin, green, exudate from which a pure culture of B. typhosus was obtained. The stool, the urine, and the Widal reaction of the blood were negative.

J. D. WILLEMS.

BRONCHITIS AND PERIBRONCHITIS AMEBIANA. WALTER HABERFELD, München. med. Wchnschr. **74**:1834, 1927.

A woman, aged 23, had had a chronic lung disease since the age of 11. Amebae in large numbers were found in the expectoration. Spores and vegetative forms were not found in the feces, but the author regards a latent bowel infection as the provoking focus.

E. F. HIRSCH.

GAS BACILLUS INFECTION OF THE GALLBLADDER. K. WAHLBERG, München. med. Wchnschr. **74**:2095, 1927.

Among 1,000 patients operated on for gallbladder disease, four had an acute cholecystitis caused by a gas bacillus infection. There was no emphysematous gangrene of the vesical tissues. The acute cholecystitis may result from either an ascending or descending infection.

E. F. HIRSCH.

B. ABORTUS (BANG) INFECTION IN MAN. P. BASTAI, München. med. Wchnschr. **74**:2141, 1927.

It is difficult to differentiate between *B. abortus* and *B. melitensis* because of their similarity. Two recent epidemics are discussed, one caused by peasants contracting the disease directly form an infected herd, and another epidemic caused by eating the butter and cream from an infected cow.

R. BRENNWASSER.

SPINAL FLUID FINDINGS IN HUMAN RABIES. HANS WEBER, Ztschr. f. d. ges. Neurol. u. Psychiat. **110**:158, 1927.

In two cases there was an increased globulin and cell count but nothing specific for rabies was found.

ROY GRINKER.

ON THE EPIDEMIOLOGY OF TUBERCULOSIS. R. KORTEWEG, Ztschr. f. Tuberk. **49**: 176, 1927.

In studying 450 consecutive necropsies in Amsterdam, in about 85 per cent of adults, definite remnants of tuberculous infection were demonstrable. In 85 per cent of these cases, the site of the primary infection could be ascertained. The frequency of the primary complex in the intestines was higher in the younger adults than in older people. Primary intestinal tuberculosis in infants was, however, extremely rare. In regard to the later development of pulmonary tuberculosis, the localization of the primary complex did not seem to be of any importance. In places where primary intestinal tuberculosis is frequent, such as in Edinburgh, for example, it is mostly due to bovine infection, whereas in localities where primary intestinal tuberculosis is rare, a larger percentage of these is due to human bacilli.

MAX PINNER.

Immunology

DISCERNMENT OF HUMAN RACES BY BLOOD, PARTICULARLY OF RUSSIANS FROM JEWS. E. O. MANOILOFF, Am. J. Phys. Anthrop. **10**:11, 1927.

Blood tests of 880 Jews and, 1,120 Russians, by the author's new method, have led to the following results: The determination of different races by blood with author's reagents—in this case to distinguish Jewish blood from Russian—gave the correct result in 91.7 per cent of the cases tested. The oxidizing process was produced in Jewish blood more quickly than in Russian.

The reaction may be of value in medicolegal investigations. In mixed marriages the reaction gives indications of the influence exercised on one race by another.

AUTHOR'S ABSTRACT.

MANOILOFF'S "RACE" REACTION AND ITS APPLICATION TO THE DETERMINATION OF PATERNITY. ANNA T. POLIAKOWA, Am. J. Phys. Anthrop. **10**:23, 1927.

The results of author's blood tests on over 1,500 persons, according to the Manoiloff method, show important corroboration of the claims of this author. The tentative conclusions are that: In racially pure marriages the child's blood has the same reaction as the father's and the mother's. If the child's and the mother's blood give a different reaction, the father does not belong to the mother's nationality. If the child has a distinct race reaction which does not correspond to the mother's nationality, the father may belong to the nationality the reaction of which has been found in the child. Attention is also called to anthropometric and other methods of the identification of parentage.

ALEŠ HRDLIČKA.

THE OXIDATION AND REDUCTION OF IMMUNOLOGICAL SUBSTANCES. JAMES M. NEILL, WILLIAM L. FLEMING and E. L. GASPARI, J. Exper. Med. **46**:735, 1927. WILLIAM L. FLEMING and JAMES M. NEILL, ibid., p. 755. JAMES M. NEILL, WILLIAM L. FLEMING and E. L. GASPARI, ibid., p. 777.

The investigations deal with the immunologic properties of pneumococcus hemotoxin. The antigenic properties of the hemotoxin are destroyed by heat and oxidation without necessarily causing any loss of the antigenic properties of the "protein fraction" of the pneumococcus.

A NOTE ON ANAPHYLACTIC BEHAVIOR IN THE PARAMECIUM. S. G. RAMSDELL, J. Immunol. **14**:197, 1927.

Paramecia were sensitized by treatment with an anti-egg-white serum, and the response on treatment with egg-white was shown to be analogous to that in the sensitized smooth muscle. Likewise, the reaction to dilute barium chloride solution was strikingly similar to the anaphylactic response, suggesting the contractile substance as the mechanism of the reaction.

AUTHOR'S SUMMARY.

THE EXOTOXINS OF THE HEMOLYTIC STREPTOCOCCI. J. SMITH, J. Path. & Bact. **30**:651, 1927.

The principal result of the work described in this article is the conclusion that all strains of hemolytic streptococci produce exotoxins that are identical.

THE ANTIGEN IN COMPLEMENT FIXATION IN TUBERCULOSIS. MAX PINNER, Tubercle **8**:415, 1927.

As the result of the study with a large number of antigens it is pointed out that the purified alcohol soluble antigens do not yield any better results than crude alcoholic extracts, although their specific range is vastly greater than that of most routine antigens. The importance of the antigen for diagnostic tests is much overrated, and accurate technic is considered more important. The relative failure of serodiagnostic methods is explained by the insignificant part that humoral antibodies play in tuberculosis. They do not indicate resistance, and may be found in persons infected only with tuberculosis and without clinical disease; they are frequently lacking during the course of an

active disease and are considered but "witnesses of infection" (Calmette). The active antigens in vitro, both the alcoholic extracts and the carbohydrates elaborated by Zinsser, Mueller and by Laidlow and Dudley, do not have any tuberculin action on tuberculous patients or animals. The most active and most purified tuberculins isolated from culture broth (Long and Seibert, Mueller) and from tubercle bacilli (Johnson and Coghill) do not react with natural tuberculosis serum in vitro. This strict dissociation of biologically and serologically active substances in the bacillus is one of the most significant facts brought out by the attempt to analyze the antigenic structure of the tubercle bacillus. Regarding the chemical nature of the alcohol-soluble antigens nothing can be stated, except that they are apparently not proteins.

H. J. Corper.

Rôle of the Skin in the Production of Antibodies, Anaphylaxis and Anti-anaphylaxis. E. Klukhine, Ann. de l'Inst. Pasteur **41**:1108, 1927.

Following the cutaneous application of certain antigens, antibodies are elaborated in the serum only when the epidermis presents marked alterations; guinea-pigs may thus be sensitized to horse serum. With animals sensitized parenterally to horse serum, a true anaphylactic shock is not produced when the following injection is made subcutaneously. Sensitized guinea-pigs take an antianaphylactic vaccination by the procedure of Besredka, i. e., simple application of the serum to the scarified skin.

Author's Summary.

Physicochemical Nature of Diphtheria Toxin and Anatoxin. V. Koulikoff and P. Smirnoff, Ann. de l'Inst. Pasteur **41**:1166, 1927.

Acid precipitation of toxin gave precipitates having minimum lethal doses of 0.0000006 to 0.00000028 Gm.; anatoxin thus precipitated was capable of immunizing in a dose of 0.00005 Gm. The toxicity of a solution of precipitate rapidly disappears even at 5 C. and a new precipitate forms. This neutralization of toxin and formation of a second precipitate is discussed.

M. S. Marshall.

Vaccination with BCG in Guinea-Pigs. P. P. Dwijkoff and L. P. Masourowski, Ann. de l'Inst. Pasteur **41**:1194, 1927.

In guinea-pigs vaccinated with BCG and subsequently infected with a virulent strain of the tuberculosis bacillus, a process which tends toward sclerosis develops, the lesions regressing considerably and occasionally disappearing altogether. All organs give this reaction, differing only in degree. The lesions are most marked in the lymphatic ganglions and in the liver and are least marked in the spleen and in the lungs. The tendency toward sclerosis (especially in the lungs) explains the retardation one observes in certain cases in the evolution, but the prognosis remains grave. Animals inoculated successively with two virulent strains, the second more virulent than the first, always show extended lesions.

M. S. Marshall.

Study of Streptococcic Toxin on Animals of Different Species. Etienne Burnet, Arch. d. Inst. Pasteur de Tunis **16**:233, 1927.

In a large series of tests on rabbits, horses and goats with scarlet fever streptococci and toxin prepared according to the Dick formula except for the use of blood from the particular species to be tested, the rabbit was little susceptible and reacted distinctly only to a substaneous injection in the ear

and even then with two great irregularity for use in the routine titration of antiscarlatinal serums; the horse reacted locally to an intradermal injection of toxin without erythema but with an edema which appeared to be a nonspecific reaction to the bacterial protein, and was not suppressed by immunization with either toxin or organisms; and the goat reacted to toxin injected intradermally with an erythema which was due apparently to the toxin and was suppressed by immunization, and also with an edema which again was attributed to the bacterial protein, which resisted immunization and possibly indicated a state of sensitization. The difficulties of obtaining specifically reactive white goats and of comparing reactions in goats with reactions in children were, however, objections to the use of goats for the titration of antiscarlatinal serums. The lack of infection in the animals receiving such large amounts of filtrate was considered as evidence against the presence of a filtrable form of the streptococcus. The limited understanding of the nature of the toxin and the failure to produce scarlet fever in species other than man were emphasized as obstacles to the convincing demonstration of the causative agent of scarlet fever, whether a streptococcus or a virus adherent to the streptococcus but distinct from it.

ETHEL B. PERRY.

STREPTOCOCCUS TOXIN IN STRANGLES. J. LADOVSKY, Rev. de microbiol. et d'epidémiol. **6**:376, 1927.

A strangles toxin is present in blood-broth cultures of the strangles streptococcus. This toxin causes cutaneous reaction in the majority of colts, but after recovery from strangles insusceptibility to the toxin develops and the serum becomes antitoxic.

THE BLOOD CROUPS IN MENTAL DISEASES. A. PILCZ, Jahrb. f. Psych. u. Neurol. **45**:120, 1927.

In the blood grouping of psychopaths and epileptoid patients, group 3 (*B*) reaches its highest percentage. Increased precentages for groups 1 (*AB*) and 3 (*B*) are found among the hereditary degenerative psychoses, and persons of these groups, especially of group 3 (*B*) more frequently have the constitutional characteristics associated with these dispositions. This is not true for paralytic psychosis and dementia praecox and only slightly indicated for arteriosclerotic and senile psychoses.

PERORAL IMMUNIZATION WITH KILLED B. DIPHTHERIA. W. POCKELS, Klin. Wchnschr. **6**:2137, 1927.

Twenty-eight of thirty-two children were rendered "Schick-negative" in from four to seven weeks by the oral administration of killed diphtheria bacilli. The immunity is only slight. Possibly the tissue immunity is greater.

E. F. HISCH.

FORSSMAN'S ANTIGEN AND FORSSMAN'S ANTIBODY. W. FREI and SELMA GRÜNMANDEL, Klin. Wchnschr. **6**:2412, 1927.

Intracutaneous injections of Forssman's antiserums stimulate a characteristic hemorrhagic inflammation in dogs and usually in guinea-pigs, especially in young animals. Other animals of the so-called guinea-pig group, such as the cat, mouse and chicken, do not show reaction, neither do the animals of the rabbit group (monkey, rabbit and rat) that were tested. In the animals mentioned in the guinea-pig group, the content of the skin in Forssman's antigen

was approximately the same; in the guinea-pig it was somewhat less than the content of the kidney. With animals of the rabbit group it was not possible after active immunization with Forssman's antigens to stimulate heterophile reactions of the skin by intracutaneous injections of antigen; neither was it possible to do so by passive immunization. In a child, actively immunized with goat milk, a suggestive reaction appeared.

AUTHORS' SUMMARY.

CUTANEOUS REACTIONS WITH RELATED SUBSTANCES AND CUTANEOUS MULTISENSITIVITY IN ASTHMA PATIENTS. K. H. BAAGÖE, Klin. Wchnschr. **6**:2466, 1927.

Among eighty-eight patients with asthma who gave positive skin reactions, some reacted with only one, others with several antigens. Some of these reactions are probably due to the biologic relationship of the antigens and are designated "related reactions" or "group reactions." In some of the patients there seemed to be a sensitiveness toward several antigens.

AUTHOR'S SUMMARY.

PREVENTIVE INOCULATION AGAINST TUBERCULOSIS WITH CALMETTE'S B C G. F. GERLACH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:256, 1927.

Gerlach tested three strains of B C G against guinea-pigs, rabbits and goats and found that the organism is not completely avirulent, as claimed by Calmette and Guerin, but that definitely tuberculous lesions were produced, which, however, tended to heal spontaneously. Four plates show the gross and microscopic appearance of the lesions.

PAUL R. CANNON.

SERUM STUDIES ON ISOLATED VASCULAR PREPARATIONS OF NORMAL, ANAPHYLACTIC AND TUBERCULOUS ANIMALS. E. FRIEDBERGER and S. SEIDENBERG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:276, 1927.

The authors describe their methods of preparing vascular systems of guinea-pigs, rats and rabbits for perfusion tests, and their results under various conditions. Perfusion of such preparations with active or inactivated serums of the same species cause a contraction of the vessels. This effect is removed by perfusion with Ringer-Locke solution, after which the preparation can be used again. Foreign serums parallel the in vivo effect, in general. Inactivation, however, leads to a weakening or disappearance of the contracting effect. The toxicity of the serums in the vessel preparations is usually dependent on the coagulation method, i. e., clotting at a high temperature gives a toxic serum. Dialysis of normal serum or carbon dioxide passage causes the globulin to be nontoxic and the albumin, toxic.

In previously sensitized animals, doses of normal serum which in normal animals are without effect, exert a marked constricting action. Anaphylaxis is specific and it is easy to differentiate the primary toxicity of the serum from the anaphylactic reaction. Corresponding tests with heterogenetic antiserums were done. Vessel preparations of tuberculous guinea-pigs perfused with tuberculin gave a dilatation.

PAUL R. CANNON.

THE DETERMINATION OF THE NATURE OF DIPHTHERIA TOXIN AND ANATOXIN BY MEANS OF THE PRECIPITATION METHOD. E. HOEN, L. TSCHERTKOW and W. ZIPP, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:349, 1927.

This is a technical discussion of the authors' methods of testing diphtheria toxin and anatoxin by the ring test.

PAUL R. CANNON.

THE INFLUENCE OF COBRA VENOM ON THE LIPOID-ANTIBODY ACTION. ALBERT SIMEONS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:369, 1927.

The cobra venom activating function of lecithin is not influenced by the interaction of lecithin with antilecithin serum. After the flocculation of lecithin with antilecithin serum, the cobra venom activating function of lecithin is demonstrable in the precipitate. Cholesterol can restrain the damaging action of cobra venom to a marked degree. The results suggest to the author that the serologic syphilis reactions are the result of lipoid antibodies.

PAUL R. CANNON.

THE COMPLEMENT-FIXATION REACTION IN GLANDERS. S. M. BRIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:392, 1927.

Brin discusses the problem of the nature of complement and assumes that complement consists of at least two components, viz., an end piece, found in the albumin fraction of the serum and a middle piece, found in the globulin part. Using glanders serum and organisms, the author, by complement-fixation tests, studied the rôle of these components and concludes that in the Bordet-Gengou reaction the end piece is fixed, while the middle piece remains free in the solution.

PAUL R. CANNON.

THE BIOCHEMISTRY OF ANTIGENS. F. PRZESMYCKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:408, 1927.

The author, using the Zinsser technic, obtained protein free residue antigens from *Proteus* X 19 H and from typhoid bacilli. These substances reacted strongly specific with antibodies obtained by injection of the whole bacteria; the immunization, however, with them, or with them combined with swine serum, as a haptene, did not give any antibody response. Strong complement-fixation reactions were obtained with the aid of bacterial lipoids and swine serum. Antibodies produced through the injection of whole bacteria react specifically in the complement-fixation reaction with different bacterial lipoids.

PAUL R. CANNON.

EXPERIMENTS IN ORAL IMMUNIZATION AGAINST DIPHTHERIA. H. DOLD and W. WEYRAUCH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:458, 1927.

The authors attempted to immunize rabbits against diphtheria toxin by oral administration. They used fifty adult rabbits with diphtheria toxin with and without sodium benzoate, toxin antitoxin with and without sodium benzoate, and fed them the mixtures ten times over a period of three and one-half months. At the end of this time, however, they were unable to demonstrate a trace of antitoxin in any of the animals.

PAUL R. CANNON.

THE RELATIONSHIP OF PRECIPITIN AND ANAPHYLACTIC ANTIBODY TO THE PROTEIN FRACTION OF RABBIT IMMUNE-SERUMS. R. DOERR and C. HALLAUER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:463, 1927.

The authors succeeded, by electro-ultrafiltration, in quantitatively separating the precipitin and anaphylactic antibodies of immune rabbit serum with the euglobulin fraction, showing that the view that the anaphylactic antibodies are in the pseudoglobulin fraction is incorrect. It was not possible by any method of serum fractionation, to separate the precipitating effect from the passive anaphylactic effect. The union between antibodies and serum globulin is a loose and reversible one.

PAUL R. CANNON.

EXPERIMENTS WITH EEL SERUM IN ISOLATED VESSEL PREPARATIONS OF NORMAL AND PREVIOUSLY TREATED ANIMALS. TOMOMICHI TAKASAKA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:482, 1927.

Takasaka, using the Friedberger method of vascular preparations, tested the effects of perfusion of eel serum in normal and previously treated guinea-pigs as well as the isolated rabbit's ear. In normal animals, eel serum produced a marked effect, but did not have any effect when inactivated. Eel plasma is almost as toxic as the serum. Treatment with kaolin tends to remove the toxic action of the eel serum. The toxic principle resides in the albumin fraction. In previously treated animals, the anaphylactic effect is marked; anti-anaphylaxis was not obtained. There was also a marked parallelism between the vessel constricting and the hemolytic effects.

PAUL R. CANNON.

PREVIOUS TREATMENT OF NORMAL GUINEA-PIGS WITH SERUM ALBUMIN PLUS TUBERCULIN. WALTER KELLER and WERNER DÖLTER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **52**:1, 1927.

The simultaneous injection into guinea-pigs of a mixture of active swine serum plus old tuberculin sensitizes them so that a later intravenous injection of old tuberculin causes fatal shock within a few minutes. Similar treatment with swine serum globulin plus the dry tuberculin of Höchst leads, on intravenous injection of the latter alone, to fatal shock. The theoretical possibilities are discussed.

PAUL R. CANNON.

THE RÔLE OF THE ECTOPLASMS AND ENDOPLASMS OF THE MOUSE-TYPHOID BACILLI IN IMMUNITY REACTIONS. E. SPRINGERT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **52**:25, 1927.

Springert finds that the mouse-typhoid bacilli possess two antigens, ectoplasmic and endoplasmic, which are demonstrable by the agglutination and complement-fixation reactions. The endoplasmic antibodies are more effective for the bactericidal effect. Mice injected with a mixture of ectoplasmic and endoplasmic antigens are better protected than ones injected with endoplasmic antigens alone.

PAUL R. CANNON.

THE HETEROGENETIC ANTIGEN IN ANIMAL ORGANS. K. A. FRIEDE and F. T. GRÜNBAUM, Ztschr. f. Immunitätsforsch. u. exper. Therap. **52**:50, 1927.

The writers state that the organs of animals of the guinea-pig type contain not only the heterogenetic antigen of the sheep, but also those of the hen, turtle and cat. Those of the rabbit type contain neither the heterogenetic antigen of the sheep, nor of the hen, cat or turtle. The presence of the sheep antigen in the organs of the animals mentioned indicates the presence of the species antigen of the hen, turtle and cat and vice versa; if one of the antigens is absent, so also are the others.

PAUL R. CANNON.

AN AGENT WHICH CHANGES THE ISO-AGGLUTINATING POWERS OF RED BLOOD CELLS. OLUF THOMSEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **52**: 85, 1927.

By allowing group O blood to stand at room temperature for about twenty-four hours, Thomsen demonstrated an agent of unknown nature which can change the blood cells of all four types in the course of from fourteen to twenty-five hours so that they are agglutinable by all serums, even AB cells

by their own serum. This substance forms best from a few degrees above 0 C. to 20 C. At 37 C. the formation is less. The agglutination of the "changed" blood cells is due to a third agglutinin, which is effective only with "changed" corpuscles. The serum of the new-born is either poor or lacking in this agglutinin.

PAUL R. CANNON.

THE QUANTITATIVE RELATION BETWEEN ANTIGENS AND THE MAXIMUM PRODUCTION OF PRECIPITIN. I. ASAI, Acta dermat. (Japanese) **10**:165, 1927.

The amount of precipitin produced after intravenous injections of white of egg seemed to be the same whether 0.1, 10 or 30 Gm. of white of egg were injected. Generally, the precipitin reached its maximum after three injections, at intervals of ten days, as determined by tests immediately before each injection.

Tumors

PROGNOSIS AND TREATMENT OF GIANT-CELL SARCOMA. W. B. COLEY, Ann. Surgery **86**:641, 1927.

Follow-up studies have shown that "giant-cell sarcomas" are not always benign. The importance of making a prognosis and the method of treatment is at once apparent. Biopsy examinations are valuable, but if made, the whole tumor should, at that time, be thoroughly curetted down to healthy bone. The tendency of these tumors to bleed must be borne in mind. In tumor of the pelvic bones, Coley warns of the infrequency of benign tumors in them and advises the use of radium and toxins rather than curettage. With regard to toxins, he states: "If it is possible to eradicate extensive tumors and to effect a permanent cure by the use of the toxins alone without curettage, as our series of cases proves, then there is certainly strong theoretical grounds for using the method as a routine measure after operation. The end-results in the cases thus treated support this view."

Because of the 20 per cent error in relying on roentgen-ray and clinical diagnosis, the treatment for these tumors by radiation only is unsatisfactory. In his opinion, the best results are obtained by surgical intervention and toxins and possibly one radium pack treatment. A definite cure in cases of giant cell sarcomas may be obtained by radiation, but the treatment must be prolonged. The number of cases on record is too small to compare with the results of surgical procedures.

N. ENZER.

SOME PHYSICOCHEMICAL AND BIOCHEMICAL ASPECTS OF MALIGNANT NEOPLASMS. W. C. M. LEWIS, J. Cancer Research **11**:16, 1927.

The article represents a scholarly review in which the British scientist attempts to correlate some physicochemical and biochemical aspects of cell activity in malignant disease. He dwells at some length on the following subjects: The electrical properties and permeability of cell contents and membranes; the rôle of calcium, of phosphatides and of cholesterol in relation to reversible permeability; the reaction of tissue and blood in malignancy and its probable significance in connection with lead iron concentration; the antitryptic activity of blood in malignancy and the probable rôle of phosphatide or phosphatide protein complexes. He analyzes many other problems involved in the study of malignant disease which cannot be abstracted. He also gives a brief account of the nature of the lead suspension employed in Liverpool in the treatment for cancer.

B. M. FRIED.

THE RELATION OF HEREDITY TO SPONTANEOUS THYROID TUMORS IN MICE. STUDIES IN THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS TUMORS IN MICE, 25TH REPORT. MAUD SLYE, J. Cancer Research **11**:54, 1927.

The chief motive of this study is an attempt to elucidate whether or not heredity bears the same relation to the tendencies to resistance and to susceptibility to tumors of the thyroid which Slye has found to bear to tumors in other organs. The investigation was performed on 61,700 mice. Of this number of animals on which necropsy was performed, enlargement of the thyroid was found in only twenty-three mice. The microscopic investigation of the thyroids disclosed four simple colloid goiters, two papillary adenomas and seventeen malignant tumors. Eleven of the malignant thyroid growths have occurred in one small strain of Japanese waltzing mice, consisting of 133 members. The eleven cancers of the thyroid have occurred in classic accordance with the laws of heredity for a mendelian recessive. Thus heredity, states Slye, is shown to be an unquestionable fact in the occurrence of these cancers of the thyroid. The tendency to resistance to them is shown to be dominant over the tendency to susceptibility, and the mendelian ratio is closely approximated. The results obtained are in exact accord, in every respect, with all other studies of cancer heredity in Slye's laboratory which have concerned themselves with organs other than the thyroid. Analogous to cancer of the thyroid in man, irritation could not be assigned as a factor causing cancer of the thyroid in mice.

B. M. FRIED.

THE NATURE OF ATROPHY AND HYALINIZATION OF CELLS AND TISSUES. M. T. BURROWS, J. Cancer Research **11**:72, 1927.

Burrows attributes the precancerous atrophies and hyalinization to the removal of ergusia from the cells and tissues (ergusia is a term coined by Burrows to designate a lipoidlike substance or substances present in the tissues). Previous experiments have shown to him as well as to Jorstad that the ergusia is closely related or identical to the fat-soluble vitamins of the tissues. He assumes, therefore, that hyalinzation and atrophy are the result of the loss of these vitamins from the cells and tissues.

B. M. FRIED.

A CLINICAL STUDY OF THE EFFECT OF RADIATION ON BLOOD CHOLESTEROL IN MALIGNANT DISEASE. W. L. MUTTICK and R. BUCHWALD, J. Cancer Reearch **11**:86, 1927.

The authors have investigated the blood cholesterol of thirty-six patients selected from the ordinary run of dispensary cases. Blood was taken from the arm vein and collected into oxalated tubes, four hours after the patient had had a light breakfast. The treatment was given by high powered roentgen ray, radium or both agents combined. The blood was examined after an overnight fast of fourteen hours. The methods of Myer and Wardell for the analysis of the blood cholesterol were used.

The results obtained are to the effect that the cholesterol level decreases after radiation treatment, but tends to return to its preradiation figures after a certain lapse of time. The decrease in the blood cholesterol following irradiation is not proper to malignant disease only, but is also observed in nonmalignant diseases. The blood cholesterol values are identical in persons with and without a malignant condition.

B. M. FRIED.

A Study of the Influence of Radiation on Cholesterol in Vitro. M. C. Reinhard, J. Cancer Research **11**:95, 1927.

A solution of cholesterol in chloroform is changed chemically by short wave-length radiation. Filtered radiation produces the same amount of change or unfiltered radiation. Therefore, it must be the shorter wave-length which is effective. The amount of change is dependent on the condition of the solute in a dissociated form. This change in vitro is much less than in vivo.

B. M. Fried.

Tumor Massage and Metastases in Mice. M. C. Marsh, J. Cancer Research **11**:101, 1927.

Surgeons have observed that malignant tumors occasionally show widespread metastases following an attempt to remove the new growth. This was attributed to the fact that during the operation clumps of tumor cells have probably penetrated into the circulation thus being transported to different parts of the body. In the laboratory, Tyzzer called attention to the fact that massage of a transplanted carcinoma in Japanese waltzing mice is followed by an increase in the percentage of mice bearing metastases. March investigated the relationship between massage and the dissemination of the growth in spontaneous tumors. His conclusions are that violent, long continued massage of spontaneous mammary tumors in fifty mice increased the percentage of mice bearing microscopic metastases from forty to sixty-two. These mice are refractory to massage as a means of disseminating tumor cells. From this investigation, it would appear that manipulation of a malignant growth is a dangerous procedure in human cancer.

B. M. Fried.

A Study of Sarcoma of the Fowl Produced by Arsenic and Embryonic Pulp. A. W. M. White, J. Cancer Research **11**:111, 1927.

Carrel produced evidences that arsenious acid mixed with chicken embryonic pulp in a few days, in the fowl leads to the transformation of normal tissues into fibrosarcomas which contain a filtrable principle analogous to the agent of Rous. He assumed that there is a formation of the tissues under the influence of a nonspecific chemical substance, of a principle which resembles a virus, acts in a specific fashion on the cells of a certain type, and reproduces itself indefinitely in the presence of these cells.

White's experiments along the same lines have shown that the injection of dilute arsenious acid and embryonic pulp leads to the formation of a sarcomatous growth as it was described by Carrel. The tumor can be reproduced by the use of Mandler filtrates, by implantations of small fragments of frozen neoplastic tissue and by injection of small amounts of dried tumor. The original tumor, according to White, arises from the embryonic pulp and not from the tissues of the host.

B. M. Fried.

Tumours of the Rabbit. Cyril J. Polson, J. Path. & Bact. **30**:603, 1927.

The tumors of rabbits previously reported are grouped according to structure and to site and fourteen new cases are described, four of them being adenocarcinoma of the uterus.

NEUROBLASTOMA SYMPATHICUM. M. MEUNIER, Arch. de méd. d. enf. **30**:569, 1927.

The sympathicoblastoma has been mistaken for a round cell sarcoma. It originates where there are sympathetic neuroblasts, in three fourths of the cases from the medullary portion of the suprarenals. Its point of origin is almost invariably in the abdomen. Metastases are usually found in the liver, bones and lymphatic glands. If death does not supervene at an early stage, multiple metastases develop in the cranial bones, accompanied by a characteristic exophthalmos.

The microscopic picture is characterized by (1) lymphocytoid elements, recalling sarcomatous cells; (2) multinuclear giant sympathicoblasts; (3) neurofibrils with accumulations of nuclei, arranged in "rosette" form. Hemorrhages and necroses are frequent within the foci.

The clinical diagnosis can only be made when the skeleton, and more especially the cranium is attacked. If confined to the abdominal stage, the disease cannot be diagnosed.

A. LOW.

SARCOMA AFTER WAR INJURIES. E. MELZNER, Arch. f. klin. Chir. **147**:153, 1927.

The injuries of the last war have given rise to very few sarcomas. On the other hand, numerous clinical cases have been reported in which the relationship cannot be denied. They suggest the possibility that in specially predisposed persons trauma may serve as the determining factor. Melzner reports the case of a man who sustained an injury to the left thigh during the war. The limb had to be amputated eleven years later because of a fibrosarcoma which had developed at the exact site of the injury.

MALIGNANT TUMORS CAUSED BY TAR. B. MARTIN, München. med. Wchnschr. **74**:753, 1927.

Small lumps of tar were introduced intracutaneously into thirty-eight animals after they had been treated intravenously wth a tar preparation for several months. Twenty-one of these developed malignant tumors. An equal number of control animals, not treated intravenously beforehand, did not develop tumors.

J. D. WILLEMS.

THE BIOLOGIC TREATMENT OF CARCINOMA. A. THEILHABER, München. med. Wchnschr. **74**:1087, 1927.

The treatment consists of transplanting fresh tissue from the spleen or thymus gland of the rabbit or the calf into the abdominal wall of patients with carcinoma. In 85 per cent of the cases there is cessation or regression of growth of the tumor with other beneficial results. There are no complete cures.

J. D. WILLEMS.

CARCINOMA OF THYMUS. RALF KAIJSER, Acta path. et microbiol. Scandinav. **4**: 221, 1927.

Two cases in men, about 70 years old, are described. The malignant tumors of thymus are grouped as (1) sarcomas from the capsule or underlobular connective tissue, (2) round cell or lymphosarcomas which originate from the round cells of the thymus and practically indistinguishable from similar tumors from lymph nodes, and (3) carcinomas, which are the most frequent thymic tumor and come from the epithelial reticulum of the thymus. The cases of carcinoma of the thymus in the literature are brought together and discussed.

Medicolegal Pathology

ACUTE CARBON MONOXIDE POISONING IN A BURNING BUILDING. E. GELMA and C. SIMONIN, Ann. de méd. lég. **7**:173, 1927.

The bodies of two persons entrapped in a burning building were excessively burned, and the bodies of two others, only superficially. With blood taken from the hearts of all four bodies, the degree of saturation with carbon monoxide was found to vary from 77 to 89 per cent, an average of 84 per cent. From this it was concluded that death of all four was due to carbon monoxide and not to burns; also that the burns of at least two of the bodies must have occurred after death.

E. R. LECOUNT.

SUICIDE BY SMOTHERING. E. ROSSELT, Ann. de méd. lég. **7**:222, 1927.

Absence of the minute hemorrhages in the serous coverings of the thoracic viscera, "Tardieu's spots," characteristic of suffocation is explained by the slowness with which death occurred after the deceased had wrapped a rain coat tightly about his head and neck and tied it on tightly. The hyperemia of the trachea produced an appearance resembling granite.

In the records of the Institute of Legal Medicine at the University of Geneva where the body was examined, death from suffocation was recorded only nine times, and in none of these cases was the smothering due to suicide.

E. R. LECOUNT.

HEMOPHILIA AND OCCUPATIONAL ACCIDENTS. FAUQUEZ, Ann. de méd. lég. **7**: 237, 1927.

Considerable discussion at a meeting in April, 1927, of the Societé de Médicine Légale de France (a society now 60 years old) followed the report of the death of a young apprentice after six days of bleeding from an injury received while at work. The discussion centered about the liability for his death. Evidence of hemophilia was not obtained in others of his family or ancestors. All modern methods of promoting coagulation failed to check the continuous oozing from the wound resulting from the traumatic loosening of an incisor tooth.

With the report are many details obtained after his death of a number of close approaches to death from bleeding due to trivial injuries as far back as the age of 3 years.

E. R. LECOUNT.

INDUSTRIAL ACCIDENTS FROM ELECTRICITY. F. NAVILLE and G. DE MORSIER, Ann. de méd. lég. **7**:245, 1927.

Modifications in industry which introduce new hazards have always resulted in an increase of deaths and injuries demanding a refurbishing and enlarging of views previously held concerning the harmful factors. The growing extension of the use of electrical power has in its turn brought with it a great increase in the number of maimed and killed and a lively interest in the entire subject of electrical casualties. The laboratory experiments on which depend our knowledge of the action of electricity on animals, the clinical effects and pathogenesis of electrocutions, the conditions responsible for the severity of the accidents and their medicolegal relations are presented in a comprehensive review. Of the two modes of death, asphyxia and syncope, the authors emphasize the importance and frequency of the latter, as well as the fibrillation and tonic spasm of the heart muscle with which it may be associated.

The alternating current is regarded as the more dangerous. It causes convulsions, contracted hands, persistence of passage of the current through the body and damage of the heart. The continous current inhibits action of the nervous system more strongly. There are no lesions which explain death. The minute hemorrhages in the lungs, myocardium and brain and the hyperemia of the viscera in general are ascribed to abrupt intravascular hypertension.

E. R. LeCount.

Bullet Wounds of Entrance. R. Piédelièvre, Ann. de méd. lég. **7**:283, 1927.

This article should be familiar to every one who is interested in bullet wounds. It is based on study of such wounds in living and dead human and animal tissues, and many substances such as putty, paraffin, sheets of rubber and paper. Its chief merit lies in the clear explanation of features bullet wounds possess due to the characteristics of the skin. The epidermis which is not elastic is rubbed off from the lining of the sac made when the elastic corium is driven in previous to its penetration by the bullet. As a result the hole in the corium is surrounded by a zone of bare corium when the skin rebounds to its former level after the bullet has passed on.

The size of this zone depends on several factors among which the shape of the front end of the bullet is important, for blunt bullets push the corium ahead of them farther before penetration than sharp nosed bullets and the deeper the sac, the larger the zone of erosion. This zone has sometimes been referred to as the "brand" and is frequently mentioned as a buried area. Piédelièvre has examined this bared corium carefully and failed to find evidence of burning as a rule. The heat accompanying the explosion, as is well known, as a rule is insufficient to ignite wads of felt or cotton. It is not sufficient to warm the central core of lead in metal-jacketted bullets. The heat due to friction of the barrel lining is quickly lost in the air. This collar of erosion about the bullet hole is often blackened with smoke and scales of metal. With bullets from unclean barrels, the blackening is greater. Its appearance immediately after the shooting is different than later if blood accumulates, then clots, and has time to undergo further changes before examination. The sharper the nose of the bullet, the smaller the hole in the center of the zone of absent epidermis as compared with the caliber of the bullet.

An example of the care used in confirming conclusions by experiments is the result obtained by firing bullets through a sheet of rubber with a coat of dried glue on its back. All about the wound of exit, there were rings where the glue had cracked, much like the rings of waves which form on the surface of water when a stone is thrown in. Associated with it such wavelike rebounding of the corium to its former shape are rings where the bleeding is greater about the bullet wounds of the skin.

Matters of oblique entrance, powder stains and wounds, the microscopic appearance of powder found in wounds and the chemical reactions which may be obtained to identify its character, the manner in which clothing is carried into wounds, and the relation of microscopic conditions in wounds to the time that life may have persisted after death are some of the other phases of bullet wounds discussed, all with a great deal of attention to control experiments. It is evident that a large fund of information is gathered at the Legal Institute in Paris from the careful study of bullet wounds and that application of the knowledge acquired finds great practical usefulness.

E. R. LeCount.

ELECTROCUTION WITH A CURRENT OF 12,000 VOLTS. T. SIMONIN, Ann. de méd. lég. **7**:339, 1927.

A huge burn was found on the right hand where the current entered and a burn perforation of the right groin where it emerged; there were also found four perforations of the bowel with charred edges, two of them oblong and large and two, small and circular. The man lived thirteen hours after the accident and death was attributed to absorption of tissue necrotic from burns.

E. R. LECOUNT.

SEPSIS AND RUPTURE OF THE HEART FOLLOWING AN INDUSTRIAL ACCIDENT. E. SOREL, Ann. de méd. lég. **7**:461, 1927.

While disrobing for a physical examination, a man, aged 62, suddenly died. About six weeks previously he injured one hand with a nail and the wound became gangrenous. A postmortem examination was made some weeks after death on account of insurance and a rupture of the heart found was attributed to sepsis; the coronary arteries were healthy.

E. R. LECOUNT.

ESTIMATION OF THE AGE FROM BONES. H. MERKEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **10**:256, 1927.

Disappearance of a man about 60 years of age and suspected murder led to exhumation and reexamination of the remains of a skeleton buried for four and one-half years. It was decided the bones were those of a youth because there were radiating furrows numbering from twenty to twenty-six all around the edges of both upper and lower surfaces of the bodies of the vertebrae, principally those of the thoracic and lumbar regions. Merkel was unable to find any definite emphasis of these furrows and ridges by anatomists. Apparently this is the first time their significance has been recognized.

E. R. LECOUNT.

THE IMPORTANCE OF ASCERTAINING THE CHARACTER OF DIRT IN WOUNDS. NIPPE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **10**:262, 1927.

Microscopic and chemical examinations of foreign material in the injured scalp and crevices of an unsuspected fracture of the cranial bones led to exonerating a man accused of murder. It was supposed that the assault had taken place indoors. Witnesses testified the accused remained inside and the injured man was found outside where in falling, sand and dirt become embedded in the wounds of the head he sustained.

E. R. LECOUNT.

GNAWING OF DEAD HUMAN BODIES BY HOUSE CATS. STRAUCH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **10**:457, 1927.

Occasions arise when it is necessary to decide, if possible, which animals have fed on dead human bodies. Rats and dogs are known to do so, and cats also when somewhat starved. The long tusklike teeth in cats, two in front in each jaw pierce the food and help to hold it while the teeth behind cut it in a way similar to the cutting action of shears. The pieces obtained are not ground up in mastication, but are swallowed forthwith. The edges of places gnawed by cats therefore possess marks as though pieces had been cut away with shears, and beyond the edges there are holes in pairs made by the poinard-shaped front teeth, the two holes always the same distance apart.

E. R. LECOUNT.

TYMPANUM PERFORATIONS AND DEATH FROM DROWNING. E. SCHLITTLER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **10**:470-478, 1927.

From the numerous accounts of narrow escapes from drowning experienced by good swimmers who have had attacks of severe dizziness due to water entering the middle ear through old perforations, the aiding or causing of drowning by such perforations has acquired forensic importance. The theme of this report is that single or multiple holes in the tympanum may result from post-mortem decomposition, and in a relatively short time when putrefaction occurs in water that is warm. This was demonstrated by subjecting petrous bones from human bodies to various controlled experiments.

E. R. LECOUNT.

EXPERIENCES WITH THE LEGAL USE OF BLOOD GROUPING STUDIES. HANS MAYSER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **10**:638, 1927.

The judicial recognition of the study of blood groups as evidence in cases involving questions of parentage and of the source of blood spots provokes a discussion of these points with the addition of certain data. The applicability of the accepted rule that an agglutinogen found in a child must be present in at least one of the parents, and the consequent decisions in regard to the possibility or the impossibility of a certain person being the parent of a given child, are brought out. In regard to blood spots the need of knowing the blood groups of the persons concerned (the assailant and the victim, for instance), and the need of establishing beyond question the blood group of the spot, are emphasized. The demonstration of iso-agglutinin of a blood spot in a microscopic test with from 3 to 5 per cent suspensions of blood cells of groups 2 and 3 is considered at far greater length than is the test for agglutinogens by the absorption method. In the single case mentioned no iso-agglutinin could be determined although the precipitin test for blood was positive.

THE SIMULTANEOUS SPECIFIC STAINING OF TUBERCLE BACILLI AND ELASTIC FIBERS AFTER JESSEN'S METHOD. H. AXHAUSEN, München. med. Wchnschr. **74**:365, 1927.

In this modification of Jessen's method for staining specifically tubercle bacilli and elastic fibers the sputum is heated in sodium hydroxide, applied to the slide, fixed and stained with carbol fuchsin, destained with acid alcohol and then again stained with a mixture containing hematoxylin. The results are diagnostically satisfactory.

J. D. WILLEMS.

THE PRESENCE OF SPIROCHETES IN THE SPINAL FLUID OF SYPHILITIC PATIENTS. W. SCHÖNFELD and H. KREY, München. med. Wchnschr. **74**:412, 1927.

The fluid is withdrawn, mixed with an equal volume of 95 per cent alcohol and centrifugalized at high speed. The resultant clump of sediment is embedded in paraffin and sectioned and stained. Spirochetes are then easily located by the microscope. Fifteen of seventeen fluids examined from all stages of syphilis contained spirochetes.

J. D. WILLEMS.

THE COLLOIDAL REACTION OF TAKATA-ARA IN TWO HUNDRED CASES. ERICH BLUM, Ztschr. f. d. ges. Neurol. u. Psychiat. **110**:504, 1927.

This test was found to differentiate quickly and easily syphilitic from non-syphilitic diseases of the nervous system, but it is not a substitute for the Wassermann reaction. Small amounts of blood in the spinal fluid cause a diversion of the reaction to the positive side.

ROY GRINKER.

Technical

THE RED-CELL SEDIMENTATION TEST IN CHILDREN. E. M. GREISHEIMER, J. A. MYERS, N. P. PETERSON, A. D. KLEIN and A. COLLINS, Am. Rev. Tuberc. **16**: 344, 1927.

No correlation was found between age and the sedimentation index. The latter seems higher in children than in adults. No marked differences were found between girls and boys. Weight did not seem to be a determining factor in the sedimentation test. There were few children who showed a positive Larson ring test, but these few showed a faster sedimentation than the children having negative tests. The boys having positive Piquet or Mantoux tests showed a faster sedimentation rate than those having negative tests, but the condition was reversed in the girls. No definite relationship between the percentage of hemoglobin and the sedimentation index or twenty-four hour reading was found. The latter did not appear to be related to the red cell count. The relation between leukocyte count and sedimentation rate was variable.

H. J. CORPER.

THE ACETIC ANHYDRIDE SULPHUR IN ACID TEST. FURTHER DATA ON THE BOLTZ-CEREBROSPINAL FLUID TEST. L. D. CODY, Arch. Neurol. & Psych. **18**:565, 1927.

The original Boltz test is made by placing 1 cc. of spinal fluid in a Wassermann test tube and adding 0.3 cc. of acetic anhydride drop by drop. The contents of the tube are then shaken and 0.8 cc. of concentrated sulphuric acid is added drop by drop. The tube is again shaken and observed for about five minutes, when a blue pink or lilac color will develop in positive general paralytic fluids. The author's modified Boltz test is essentially the same except that the concentrated sulphuric acid is added rapidly and not drop by drop. The Boltz test is a modification of the Lieberman cholesterol test, but observations failed to show that cholesterol is in any way responsible for the positive reactions. The modified Boltz test was used on 799 specimens of spinal fluid. Positive reactions were found in from 79 to 94.6 per cent of patients with neurosyphilis when the test had not been rendered negative by treatment. The modified test was positive in 42.4 per cent of 264 other nonsyphilitic neuropsychiatric patients. The test was found positive in 27.2 per cent of seventy-seven patients with constitutional disease occurring for the most part in patients with arthritis of the spine. The original test seems of some value in indicating the presence of abnormal processes in the meninges and the central nervous system and promises to be of real value at least equal to other routine nonspecific chemical tests. The modified test may have considerable value in the control of treatment of neurosyphilis.

T. T. STONE.

A MODIFICATION OF THE ELECTROLYTIC GUTZEIT APPARATUS FOR THE ESTIMATION OF ARSENIC IN BIOLOGICAL MATERIAL. A. E. OSTERBURG, J. Biol. Chem. **76**:19, 1928.

A modification of the electrolytic Gutzeit apparatus for the estimation of arsenic in biologic material is described. The cathode and anode chambers are separated by an alundum disk. This permits the entire sample to be placed in the cathode chamber and insures rapid and complete conversion of all inorganic arsenic to arsine.

AUTHOR'S SUMMARY.

TRYPTOPHANE REACTIONS IN THE SPINAL FLUID. B. S. WALKER and F. H. SLEEPER, J. Lab. & Clin. Med. **12**:1048, 1927.

The Boltz technic for cholesterol in the spinal fluid is as follows: To 1 cc. of the fluid to be tested add 0.3 cc. of acetic anhydride, drop by drop, with shaking. To this mixture, 0.8 cc. of concentrated sulphuric acid is added in a similar manner. After it has stood for five minutes the tube is examined against a white background, and the appearance of a blue or lilac color is considered as a positive reaction. It is suggested that the Boltz reaction may be of considerable value in estimating increases in the protein content of spinal fluid, although it cannot be considered as specific for any single clinical entity.

S. A. LEVINSON.

THE DETERMINATION OF FIBRIN IN BLOOD PLASMA. J. CHANDLER, J. Lab. & Clin. Med. **12**:1092, 1927.

One cubic centimeter of clear plasma is measured with a calibrated Ostwald-Folin pipet into a test-tube 25 by 200 mm.; 28 cc. of 0.8 per cent sodium chloride and 1 cc. of 2.5 per cent calcium chloride are added and the contents mixed and allowed to stand for at least thirty minutes. At the end of that time a rather firm jelly should be formed. The jelly is loosened by inclining and rotating the tube, and the contents are poured on a filter which has previously been moistened with 0.8 per cent sodium chloride and attached to the funnel. A glass rod drawn out to a diameter of approximately 1.5 mm. and pointed, is introduced, and by rotating the rod slowly the fibrin is collected quantitatively on the end of the rod as a firmly adhering mass. The fibrin is washed with distilled water from a wash bottle, dried with filter paper, carefully removed from the rod by means of filter paper and introduced into a 25 by 200 mm. pyrex tube graduated at 50 cc. One cubic centimeter of the concentrated digestion mixture of Folin (100 cc. concentrated H_2SO_4, 300 cc. 85 per cent H_3PO_4, 50 cc. of 5 per cent $CuSO_4.5H_2O$) is added, the mixture heated gently with a micro Bunsen burner until the fibrin is dissolved, then more strongly until the tube is filled with white fumes when a small watch glass is placed over the mouth of the tube and the heating continued for thirty seconds after the contents of the tube have become a light bluish shade with no trace of brown. After cooling for two minutes, distilled water is added to approximately 40 cc., the contents of the tube stirred with a long glass rod to break up any mass of silica formed, and the rod rinsed with distilled water. When the contents of the tube have cooled to room temperature, the volume is made up to 50 cc. with distilled water and thoroughly mixed. The contents of the tube are now poured into a 50 cc. conical centrifuge tube and centrifugalized until the silica is all precipitated and the supernatant liquid entirely clear, which usually requires from twenty to thirty minutes. Twenty-five cubic centimeters of the clear supernatant liquid are pipetted into a 50 cc. volumetric flask; 15 cc. of the Nessler's solution described by Folin and Wu (*J. Biolog. Chem.* **38**:81, 1919) are added, and the contents made up to volume, mixed and compared in a colorimeter with a standard ammonium sulphate solution, the standard being set at 20 mm. A five-tenth milligram nitrogen standard is used which is prepared by measuring 5 cc. of the standard ammonium sulphate solution described by Folin and Wu (0.4716 Gm. dry chemically pure $(NH_4)_2SO_4$ per liter) into a hundred cubic centimeter measuring flask, diluting with 60 cc. distilled water, adding 1 cc. of the concentrated digestion mixture and nesslerizing with 30 cc. Nessler's solution. If preferred, the silica may be removed by filtering through a Muncktell OB or other similar retentive filter into a 100 cc. volumetric flask, washing to a volume of about 60 cc., and nesslerizing

with 30 cc. Nessler's solution. In either case, the calculation is made as follows: Per cent plasma fibrin — Gm. fibrin per hundred cubic centimeters plasma = $\frac{\text{standard reading}}{\text{sample reading}} \times 0.5 \times 6.25$.

S. A. LEVINSON.

THE BLOOD-URINE DENSITY INDEX. D. POLOWE, J. Lab. & Clin. Med. **12**:1100, 1927.

The density of the blood is determined by the falling drop method of Barbour and Hamilton. The density of the urine is determined in the same way, or by urinometer, immediately before or after that of the blood is determined. The calculation of the blood-urine density index (B-U D I) is made by taking the values to the right of the decimal point, the blood value being divided by the urine value. Example, BD = 1060; UD = 1020; then 60/20 = 3 which is the blood-urine density index (B-U D I).

S. A. LEVINSON.

CEDAR OIL AS AN AID IN FINDING PARASITIC OVA IN FECES. G. E. HEIN, J. Lab. & Clin. Med. **12**:1117, 1927.

An extremely thick smear of the feces which is suspected to contain the organism is made on a slide and allowed to dry at room temperature. The thickness of the smear is about from five to ten times as heavy as ordinarily would be used. Cedar oil is dropped on the field and covered with a cover glass. The feces are rendered transparent and ova are greatly accentuated by the clear background.

S. A. LEVINSON.

FREEZING BCG FOR TRANSPORTATION OVER GREAT DISTANCES. C. GUÉRIN, Ann. de l'Inst. Pasteur **41**:1189, 1927.

The results were favorable, the experiments showing that enough vitality for use was retained after two months in a frozen condition. Ampules should be placed in 15 per cent aqueous glycerin solution in thermos bottles and the whole cooled at —7 C., and subsequently shipped in ice.

M. S. MARSHALL.

A SIMPLE METHOD FOR DEMONSTRATING THE CELLS OF THE RETICULO-ENDOTHELIAL SYSTEM. D. MÜNSTER, Centralbl. f. allg. Path. u. path. Anat. **40**:177, 1927.

Münster slowly injects a culture of staphylococci emulsified in 2 cc. of Ringer's solution into the femoral vein of rats and mice anesthetized with urethane or ether. From fifteen to thirty minutes later, the animals are killed and their tissues fixed in formaldehyde. Frozen or paraffin sections are then stained with cresyl violet or by Gram's method using alum carmine as a counter stain. Cocci are found in abundance in the Kupffer cells of the liver, in the phagocytic cells at the edge of the splenic corpuscles where amyloid accumulations are first seen, in the septum of the lung and endothelium of the renal glomeruli, and, at times in the endothelium elsewhere.

GEORGE RUKSTINAT.

THE ALKALI EXCRETION OF THE KIDNEY AS AN INDEX OF RENAL FUNCTION. M. ROSENBERG and A. HELLFORS, München. med. Wchnschr. **74**:926, 1927.

First 20 to 30 drops of dilute hydrochloric acid are given in 400 cc. of water and the urine collected every half hour for two hours. Then 20 Gm. of sodium bicarbonate are given in 400 cc. of water and the urine collected the same way. All eight samples are tested for H-ion concentration. In normal kidney function the urine will become alkaline to at least p_H 8.

J. D. WILLEMS.

Society Transactions

TWENTY-NINTH ANNUAL MEETING OF THE SOCIETY OF AMERICAN BACTERIOLOGISTS

School of Medicine and Dentistry, University of Rochester, Rochester, N. Y.

December 28, 29, 30, 1927

President, Robert S. Breed, Agricultural Experiment Station, Geneva, N. Y.
Vice-President, Alice C. Evans, U. S. Hygienic Laboratory, Washington, D. C.
Secretary-Treasurer, J. M. Sherman, Cornell University, Ithaca, N. Y.

SECTION ON IMMUNOLOGY AND COMPARATIVE PATHOLOGY (PAPERS 1-7)

F. M. Huntoon, *Chairman*

SYMPOSIUM ON "BACTERIAL TOXINS"

The Nature of Diphtheria Toxin. Arthur Locke and E. R. Main. (From St. Luke's Hospital, Chicago.)

The paper discusses: (1) the conditions which favor the production of toxin in cultures of toxicogenic diphtheria bacilli; (2) the properties and reactions of the toxin, in vitro; (3) the immunologic and histologic changes which follow its injection into animals; (4) the properties which diphtheria toxin shares in common with other toxins and with antigens in general, and (5) the conclusions which may be drawn concerning the nature of diphtheria toxin. The principal new data presented relate to the mechanism of toxin production, the preparation and properties of a highly purified toxin and the source of the latter's toxicity.

Destruction of Botulinum Toxin by Milk Bacteria. J. M. Sherman, C. N. Stark and Pauline W. Stark. (From Cornell University, Ithaca, N. Y.)

The unique freedom of milk and milk products as agents in the dissemination of botulism is of great interest. Although fresh milk may ordinarily be used before bacterial growth has been sufficiently extensive to be dangerous from the standpoint of botulinum poisoning, such is not the case with cheese and certain other milk products. Indeed, from the standpoint of chemical composition, cheese would appear to be an excellent medium for the production of this toxin. The explanation which might appear valid in that the acidity of most types of cheese is sufficiently high to inhibit the growth of *Clostridium botulinum,* but such an explanation would not hold for all types of cheese, and from some of the experimental results which have been published concerning the acid limits for growth of this organism, would indicate that a complete explanation cannot be found entirely on the basis of acidity in the case of any type of cheese. From our results on the destruction of toxins by bacteria, it appeared plausible that some of the characteristic milk organisms might have the power of destroying the toxin produced by *Clostridium botulinum.*

It has been found that *Streptococcus lactis* and *Lactobacillus casei* have the power to destroy botulinum toxin. This is of particular interest in connection with cheese, since in most types of cheese *Streptococcus lactis* is the predominating organism during the early stages of ripening, while *Lactobacillus casei* is one of the predominating organisms in all types of cheese during the later stages of ripening.

THE ACTION OF HEMATOXINS ON OXYGENATED AND REDUCED BLOOD CELLS. GUILFORD B. REED and J. H. ORR. (From Queen's University, Kingston, Ontario, Can.)

In agreement with the work of Neill, it was found that the oxidation of *B. welchii* toxin by the exposure of culture filtrates to the air resulted in loss of hematoxic action. The degree of oxygenation of the red cells with which the hematoxin is combined proves to have a similar influence on the reaction. When *B. welchii* toxin is mixed with standard emulsions of red cells which have been freshly oxygenated or reduced with carbon dioxide, from two to three times more toxin is required to produce a given amount of hemolysis in the oxygenated than in the reduced blood. Quantitative data of the influence of the degree of oxygenation are included.

A STUDY OF THE REACTIONS BETWEEN TOXINS AND ANTISERA PRODUCED WITH HEMOLYTIC STREPTOCOCCI. MARY B. KIRKBRIDE, MARY W. WHEELER and JESSIE L. HENRY. (From the Division of Laboratories and Research, State Department of Health, Albany, N. Y.)

This paper presents the results of comparative tests of the neutralization of monovalent antistreptococcus serums with the homologous and heterologous toxins as determined by intracutaneous tests on persons and goats.

A GASTRO-INTESTINAL POISON PRODUCED BY BACTERIUM ENTERITIDIS AND BY BACTERIUM PARATYPHOSUM B (AERTRYCKE TYPE). SARA E. BRANHAM, LUCILLE ROBEY and LOIS A. DAY. (From the Department of Hygiene and Bacteriology, The University of Chicago, Chicago.)

This study was made with seventeen strains of *Bacterium enteritidis* and *Bacterium paratyphosum B* (aertrycke type) which were isolated from cases of food poisoning. All of these strains produced typical fatal infection in mice, when given by mouth. The organisms could regularly be recovered and identified.

Series of mice were fed by catheter: (1) heat-killed broth cultures, (2) autolyzed suspensions, and (3) sterile Berkefeld filtrates of broth cultures. The highest mortality, 41 per cent, occurred in the group fed with filtrates. No paratyphoid organisms could be recovered from these. The autolyzed suspensions had little effect.

Curves were plotted showing the incidence of mortality, in these groups of mice, including the group fed with the living cultures. These showed that the greatest number of deaths among the mice fed with living organisms occurred on the fifth and sixth days after feeding, whereas in the group fed boiled broth cultures and filtrates, the highest death rate occurred between the tenth and fourteenth days. Mice injected intraperitoneally with the latter materials died in from two to four days. Failure to recover paratyphoid bacteria from the latter groups suggested the presence in the filtrates and broth cultures of a toxic substance the action of which is usually masked by the quicker course of infection with the living organisms.

Therefore, more than 300 mice were fed filtrates of cultures of various ages in different kinds of mediums. Constantly, a certain proportion of these mice died between the tenth and fourteenth days. They presented a uniform pathologic picture at autopsy. Paratyphoid organisms could not be recovered from them. Death did not occur in any series of mice kept under identical conditions, but fed with the uninoculated mediums.

Filtrates from cultures in different kinds of medium varied greatly in their poison content: in some a great deal of beef heart medium was associated with a mortality as high as 80 per cent; veal infusion broth was usually followed by the death of from 20 to 40 per cent; some were uniformly nontoxic. Filtrates from 24-hour cultures seemed most potent. The poison was not injured by autoclaving at 15 pounds (6.8 Kg.) for fifteen minutes.

There seems, undoubtedly, to be a heat resistant poison in young cultures of *Bacterium enteritidis* and *Bacterium paratyphosum B* (aertrycke type) which is toxic for mice when taken by mouth. This poison seems to be different from the toxic principle previously described, which acts only on intravenous injection. Whether it is a bacterial toxin or is a poison formed by the action of the micro-organisms on the medium, can be determined only by further investigation.

PROPERTIES OF A TOXIN PRODUCED BY AN ORGANISM ISOLATED IN PERIODIC OPHTHALMIA IN THE HORSE. EDWARD C. ROSENOW. (From the Division of Experimental Bacteriology, The Mayo Foundation, Rochester, Minn.)

The incidence of the isolation of the organism in periodic ophthalmia and from feeds is discussed. The effect on injection in animals of filtrates containing the toxin, especially the specific affinity for the eye, heat resistance, solubility in ether, behavior toward absorbing agents, and the preparation of an antitoxic serum in the horse are described.

SIMPLIFIED CATAPHORESIS METHODS TO ESTIMATE DIPHTHERIA BACILLUS VIRULENCE. I. S. FALK, L. B. JENSON and J. H. MILLS. (From the University of Chicago, Chicago.)

Demonstration of apparatus.

STUDIES ON IMMUNOLOGIC SPECIFICITY OF STREPTOCOCCIC ISOLATED FROM VARIOUS DISEASES OF MAN. EDWARD C. ROSENOW. (From the Division of Experimental Bacteriology, Mayo Foundation, Rochester, Minn.)

The following are the chief points which are considered: methods of preservation of viability and specificity of cultures and bacterial suspensions; methods used in preparation of immune serum; the agglutinating and precipitin reactions of the different strains on isolation after animal passage and after long cultivation on artificial mediums; comparison of immunologic specificity with specific or elective localization in animals.

MICROBIC DISSOCIATION IN STREPTOCOCCI. L. O. DUTTON. (From the Methodist Hospital, Memphis, Tenn.)

A description is given of the various types of dissociating Streptococcus colonies. The S type is established and a variety of intermediate and rough forms are considered in an endeavor to identify the true intermediates and the extreme R types. It is pointed out that dissociation in Streptococcus strains is marked, and that most of the colony forms described for other bacterial species also occur in Streptococcus colonies. Some of the morphologic cell changes accompanying the various colony changes are pointed out. The correlation between virulence and the S type, and avirulence and the R type is noted to hold true in natural spontaneous infections.

THE INTERCONVERTIBILITY OF R AND S BACTERIAL TYPES OF B. PARATYPHOSUS B BY HOMOLOGOUS IMMUNE SERUMS. M. H. SOULE. (From the Hygienic Laboratory, University of Michigan, Ann Arbor, Mich.)

Immune serums were prepared with pure strains of the "S" and "R" forms of *B. paratyphosus B* (209S, 209R, 210S, 210R, Jordan strains). Five cubic centimeter quantities of plain infusion broth containing various concentrations of immune serums were distributed in test tubes. Serial transfers of each strain were made at intervals of forty-eight hours in homologous and nonhomologous serum broth. Before making the transplants, a loop of material was removed from each culture and spread on an agar plate. These plates were incubated eighteen hours and examined for the presence of the typical "S" and "R" colonies. "R" forms appeared in strain 209 S after five serial transplants in homologous serum broth and in the 210 S strain after two such transfers. "S" types appeared in strain 209 R after the seventh transfer in homologous serum and in strain 210 R

after the sixth transfer. The number of variants in each strain increased with each successive transfer, but the cultures never became completely dissociated under these conditions; some residual "S" or "R" organisms always remained. The "R" and "S" forms produced in this manner had all of the characteristics of the original "R" and "S" cultures. No dissociation occurred in the "S" types when grown in the presence of "R" serums (thirty transfers). "S" forms appeared in the "R" strains grown in the presence of the nonhomologous serums after sixteen transfers, but the number never became large with continued serial transplanting. The most favorable concentration of serums for inciting dissociation was 10 per cent. No dissociation of the strains was observed when serially cultured in broth containing like quantities of normal serums or in plain infusion broth of *p*H 6.5, 7.4 and 7.8. Variants appeared after two weeks' incubation, when large volumes (500 cc.) of broth containing 10 per cent homologous immune serums were inoculated. No dissociation occurred during two months' incubation of like volumes of ordinary broth *p*H. Intraperitoneal injections of the original "S" cultures in large doses (500 million) were virulent for guinea-pigs. The "R" forms were nonvirulent. "S" types obtained by dissociation of the "R" types were as virulent as the original "S" cultures. Guinea-pigs immunized by the "R" form were resistant to extremely large doses of the "S" form. The "S" form was more strongly antigenic. The view previously advanced that immune serum has a marked dissociating power on its homologous germ and a stabilizing action on the heterologous culture type is again demonstrated in this work. Similar studies with other organisms are in progress.

MICROBIC DISSOCIATION OF THE TUBERCLE BACILLUS. S. A. PETROFF. (From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, N. Y.)

Four strains of tubercle bacilli have been studied, viz., Human (H 37), Bovine (B 1), Avian (A 1) and Bacillus Calmette-Guerin (B. C. G.). All of these organisms have been dissociated, and two colonies isolated, each having distinct cultural characteristics. The last organism has been more completely studied. From this organism (B. C. G.) R and S colonies have been dissociated, and the virulence, cultural characteristics, immunologic and antigenic properties have been studied. The R colony appeared to be nonvirulent, producing localized disease in guinea-pigs which eventually healed, while the S colony always led to generalized tuberculosis.

From the studies of dissociation of these various organisms, it appears that the tubercle bacillus falls in with the rest of the organisms as far as dissociation is concerned.

RATE OF BACTERIAL ADAPTATION. VICTOR BURKE and CATHERINE ULRICH. (From the State College of Washington, Pullman, Wash.)

The modification of bacteria has attained considerable importance of late. The rate of modification has received little attention. Experiments were made to determine how quickly an organism becomes adapted to a new environment.

Staphylococcus aureus was exposed to gentian violet for different periods of time. Then the increased ability of these organisms to grow in the presence of the dye was determined. The experiments demonstrated that *Staphylococccus aureus* shows increased tolerance for the dye after eight hours' exposure. It is considered that the organism can probably adapt itself in a shorter period of time than was demonstrated. The change in the organism is considered purely as an adaptation to a new environment, and is in no way associated with changes in the life cycle, dissociation of strains, selection of variants or with mutations.

RECENT CASES OF UNDULANT FEVER IN NEW YORK STATE. RUTH GILBERT and MARION B. COLEMAN. (From the Division of Laboratories and Research, New York State Department of Health, Albany, N. Y.)

In a series of fifteen specimens submitted to be examined for evidence of enteric disease, but with clinical histories more suggestive of undulant fever, the

blood serum agglutinated cultures of the melitensis-abortus group. During the course of these investigations, two laboratory infections occurred, one with *B. melitensis,* resulting in a prolonged and severe illness, and the other with *B. abortus,* followed by mild symptoms. This strain of *B. abortus* was far more virulent for guinea-pigs than the strain of *B. melitensis.*

THERMAL DEATH POINT STUDIES OF BRUCELLA ABORTUS. C. M. CARPENTER and RUTH BOAK. (From the Diagnostic Laboratory, New York State Veterinary College, Cornell University, Ithaca, N. Y.)

Human, porcine and bovine cultures of *Brucella abortus* grown in milk and Hiss serum water were exposed to temperatures of 140, 142 and 160 F. for various intervals. The suspensions were tested for viability by making cultures and by injecting guinea-pigs. It was observed that guinea-pigs were more reliable than cultures for determining whether all of the organisms had been killed. In a few instances cultures were negative but guinea-pigs became infected. The thermal death point of cultures most virulent for guinea-pigs was higher than that of cultures which produced only mild lesions of abortion disease in these experimental animals. No cultures were viable after exposure for twenty minutes to a temperature of 140 F.

A STUDY OF ISOHEMOLYSINS. C. M. DOWNS, KENNETH KOERBER and H. P. JONES. (From the University of Kansas, Lawrence, Kan.)

The statement has been made that isohemolysins differ from immune heterohemolysins in that they cannot be reactivated by the addition of fresh serum. The following study deals with the nature of isohemolysins which occur in type I, II and III serums. Only 45 per cent of the persons in this series showed hemolysins for any type of cell. Hemolysins in type I serums were more frequently found for type III and IV cells than for type II cells. Hemolysins were rarely demonstrable in serum diluted more than 1 to 1. In those serums having no apparent hemolysins by the usual test, the addition of fresh active but non-hemolytic human or guinea-pig complement did not give any hemolysis. The absorption of these serums in the cold and the addition of complement to the treated cells did not give any hemolysis. The hemolysins are apparently absent rather than masked. When cells and complement are added to serum heated to 56 C., a slight amount of hemolysis only can be demonstrated; however, when the appropriate cells are used for absorption with the heated serum, washed and complement added, a fair degree of hemolysis can be obtained. The hemolysis is not so marked as in the original unheated serum. This seems to point to the occurrence of masked hemolysins in the different types of serums. Cells used for absorption in the cold are actively hemolyzed by the addition of complement. Cells absorbed from either heated or unheated serum in the cold gave no hemolysis unless complement was added.

A STUDY OF THE BLOOD GROUPS AMONG POLYNESIANS. CLARA NIGG. (From the Queen's Hospital, Honolulu, Hawaii, and the University of Kansas, Lawrence, Kan.)

In a series of 413 fullblooded Hawaiians, the following percentages of blood groups were found: Group 1—36.5, group 2—60.8, group 3—2.2, and group 4—0.5 per cent. This gives them a race index of 22.7.

Of this group 237 were examined for the agglutinogen described by Simson in his study of the third agglutinating system in human blood which was found associated with the A agglutinogen (groups 2 and 4). Among Hawaiians the incidence of this agglutinogen was 100 per cent and was never found in the absence of A (groups 1 and 3).

In a small group of fullblooded Samoans the following percentage occurrence was found: Group 1—38.8, group 2—28.9, group 3—26.3 and group 4—5.2 per cent. This gives a race index of 1.1.

A study of all available published data in regard to the race index shows its inadequacy for determining interracial relationships on that basis alone, and suggests rather that the percentage occurrence of all four groups must be taken into consideration.

THE EFFECTS OF UREA ON LIVING CELLS. NOBLE P. SHERWOOD and FRANCES DUNMIRE. (From the Department of Bacteriology, University of Kansas, Lawrence, Kan.)

A wide variation occurs between species concerning the susceptibilty of their red blood cells to hemolysis by means of urea. A percentage of urea giving complete hemolysis is constant for given species, but shows marked variation between species. Species differences depends on at least two of many factors: the fragility of the blood cells and the toxicity of the urea for the cells.

ORAL, SUBCUTANEOUS, AND INTRAVENOUS VACCINATION WITH NATIVE FETAL ORGANISMS. LAVERNE BARNES. (From the State College of Washington, Pullman, Wash.)

Experiments were performed with rabbits to determine: (1) whether there are agglutinins present in normal rabbit's serum for native fecal organisms; and, (2) whether an agglutinin titer for such organisms can be induced or raised by injecting vaccine orally, subcutaneously and intravenously.

Results indicate that commonly there are no normal agglutinins for native fecal organisms, or if present, they are weak. As a result of inoculating the vaccine, it appears that the intravenous method is most efficient, and the oral method least efficient in stimulating the production of agglutinins. These results have a bearing on Besredka's theory of local immunity.

A COMPARISON OF THE EFFECTIVENESS OF VACCINATION AGAINST PASTEURELLA AVICIDA BY THE ORAL, SUBCUTANEOUS AND INTRAVENOUS METHODS. LAVERNE BARNES. (From the State College of Washington, Pullman, Wash.)

Experiments performed on chickens and rabbits were devised to compare the resistance to infection of the animals injected with avicida vaccine by the oral, subcutaneous and intravenous methods. The relative effectiveness of each method was determined by administering test doses of the virulent organisms following immunization.

The results indicate that the intravenous method is most effective in producing agglutinins for the organisms, and in bringing about actual resistance to infection, while the oral method is least efficient. These results have a bearing on Besredka's theory of local immunity.

AGGLUTININ PRODUCTION. C. A. BEHRENS and C. H. KEIPPER. (From Purdue University, Lafayette, Ind.)

The purpose of this work is to show the relationship between dosage, total amount of agglutinogen injected and the interval of inoculations. All injections were made intravenously.

Experiments were conducted in which (1) the dose was constant while the total amount of the agglutinogen injected and the interval of inoculations were varied; (2) dose and total amount were constant and the interval of injections was varied; (3) dose and frequency of inoculations were constant while the total amount was varied; (4) dose, total amount and interval of injections were constant; (5) dose, total amount and interval of injections were varied; (6) total amount was constant, dose and frequency were varied; (7) total amount and frequency were constant and the dose varied; (8) frequency of injections was constant; dose and total amount were varied.

THE PRESERVATION OF COMPLEMENT IN VARIOUS GASEOUS ENVIRONMENTS WITH SPECIAL REFERENCE TO CARBON DIOXIDE. GEORGE VALLEY (Sterling Research Fellow, Yale University) and JAMES G. MCALPINE (Storrs Agricultural Experiment Station, New Haven, Conn.).

Diluted (1:2) guinea-pig serum was subjected to the following gaseous environments: (1) hydrogen, (2) nitrogen atmosphere obtained by removal of oxygen from air by alkaline pyrogallol solution, (3) vacuum, (4) carbon monoxide, (5) carbon dioxide and (6) ordinary atmosphere (open test tube). The temperature of storage was about 10 C.

The deterioration of the complement which was stored in open tube (cotton plugged) proceeded rapidly, the serum losing its hemolytic activity in from five to six days.

In vacuum, hydrogen and nitrogen the hemolytic titer of the complement changed but slightly in eight days. During the nineteen days of storage the original titer of from 0.01 to 0.03 cc. had changed to from 0.2 to 0.3 cc.

In carbon monoxide atmosphere the original titer of 0.01 cc. changed to from 0.06 to 0.08 cc. in twenty-one days, while after twenty-nine days the complementary unit of the stored serum was greater than 1 cc.

In case of the serum treated with carbon dioxide the titer was maintained practically unchanged for twenty-nine days. In three months a change from 0.03 to 0.05 cc. was observed. From one sample which had an original titer of 0.01 cc., a titer of 0.06 cc. was obtained after 129 days in storage. The replacement of air by carbon dioxide yielded the most satisfactory and promising results, aside from ease of employment. Consequently, storing of the complement in a carbon dioxide atmosphere has been made a routine procedure in the work on infectious abortion at the laboratory of the Storrs Agricultural Experiment Station, and has been found during the past eight or nine months to be an effective and feasible means for preserving serum complement.

The method is simple and is generally carried out as follows: A small test tube containing either the diluted or undiluted complement is placed in a pint fruit jar having a tight-fitting cover. The top is placed slightly to one side, and the end of a delivery tube from a carbon dioxide tank is lowered to the bottom of the jar. Carbon dioxide gas is run in slowly under from 0.5 to 1 pound delivery pressure, and usually not less than from two to three minutes. The tube is withdrawn and the top clamped down. In order to insure complete or almost complete replacement of air, the application of carbon dioxide may be repeated, the jar resealed and placed in the ice box. By this method complement may be kept for from two to five weeks with little loss in potency.

The procedure described here furnishes a means of preserving and storing left-over diluted complement as well as fresh undiluted complement for reasonable periods of time, and thus eliminates the necessity of collecting complement daily.

THE INHERITANCE OF RESISTANCE TO THE DANYSZ BACILLUS IN THE RAT. M. R. IRWIN (Introduced by C. H. Werkman). (From the Department of Bacteriology, Iowa State University, Ames, Ia.)

A dose of 15×10^7 organisms of the Danysz bacillus injected intraperitoneally into 131 heterogeneous laboratory rats, pen inbred for eight years, produced 82.4 ± 0.21 per cent mortality. Increasing or decreasing the dose produced a direct increase or decrease in the mortality rate.

Rats of the Wistar Institute stock "A" strain, which have been inbred brother-sister for over fifty generations, when injected with the same dose, gave 98.6 ± 0.17 per cent mortality for sixty-nine animals.

Rats of the Wistar Institute "B" strain, also inbred brother-sister for over fifty generations, gave 80.6 ± 1.23 per cent mortality for 31 animals.

Survivors of heterogeneous rats, mated together, produced progeny which showed a decided increase in numbers of resistant animals, the mortality being 31.9 ± 1.06 per cent for ninety-seven animals. Survivors of this first

resistant generation, mated together, produced a second generation which showed a further increase in resistant animals, the mortality being 17.0 ± 1.06 per cent for forty-seven animals tested.

Surviving males of this first resistant generation were mated to nontested females of the susceptible Wistar "A" strain, to sisters of those that had succumbed to the injection, and produced progeny that gave 34.9 ± 2.13 per cent mortality for sixty-three animals. The results obtained in this progeny eliminate the possibility that the increased resistance for the first and second resistant generations was due to maternal transmission of passive immunity and indicates that it is largely genetic in nature.

THE INFLUENCE OF ENVIRONMENTAL CHANGES ON GASTRIC SECRETION AND INTESTINAL BACTERICIDAL FUNCTION. LLOYD ARNOLD. (From the Department of Bacteriology, University of Illinois, College of Medicine, and the State Department of Public Health, Chicago.)

The endogenous bacterial flora of the small intestine is almost constant for the mammalian animals so far investigated. The hydrogen concentration within the lumen of this tract has been found to be constant. Environmental factors, both nutritional and meterologic, as well as parasitism, cause a maladjustment of the physiologic functions and is accompanied by a change in the bacterial flora and chemical constituents of the small intestine. This change can be interpreted only as a part of the mechanism of adaptation of the organism to its environment. We are reporting differences in the bacterial flora of the small intestine obtained from a study of gastric and cecal fistulas of dogs placed on different diets and in rooms with different temperature and humidity. In the process of adaptation to these changes in environment, gastric function and the biologic bacterial regulatory mechanism of the small intestine have been studied. In a normal organism there is an autodisinfecting process in the upper half or two thirds of the small intestine that destroys the bacteria ingested and prevents the large intestinal flora from extending upward. This self-regulatory mechanism of the bacterial flora is only one of a group of functions of the splanchnic area in the normal animal. Certain changes in diet, as well as climate, can cause a loss of this bacterial killing power of the intestinal tract. This accompanies a general derangement of several physiologic functions of the body.

THE DUODENAL FLORA IN ACHLORHYDRIA. LEO RICEN, H. J. SEARS and LILLIAN M. DOWNING. (From the Department of Bacteriology, University of Oregon Medical School, Portland, Ore.)

The chief stimulus to the study of this subject lies in the growing importance of achlorhydria in the etiology of pernicious anemia and the conception of that disease as a symptom complex resulting from a slowly acting hemolytic toxin of gastro-intestinal origin.

The material for this study consisted of the duodenal contents of thirty patients who presented the condition of persistent achlohydria. Two suffered from pernicious anemia, twenty-six had anemia of the chlorotic type and only four had a fairly normal blood picture. The duodenal contents of fourteen normal persons were also studied. The material in each case was collected with the duodenal tube (Jutte's modification) after thorough cleansing of the mouth and rinsing with 1:2000 potassium permanganate, the final position of the tube in the duodenum being determined by fluoroscopic examination.

Bacteriologic examination of the material consisted only in plating on blood agar and recording the appearance of the plates, relative numbers of colonies, etc., and then identifying the various colonies.

The most striking observation was the regular appearance of a rich flora in practically all cases of achlorhydria and the almost complete absence of organisms in the specimens from the normal persons. In the achlorhydric material blood destroying organisms were extremely common and included

hemolytic streptococci and staphylococci as well as hemolytic *B. coli* and other gram-negative bacilli. Green producing streptococci and other green producing colonies were observed frequently. *B. alcaligenes* was noted several times, pneumococci twice and gram-negative diplococci occasionally. *B. coli* was prominent in both the cases of pernicious anemia.

Persistent achlorhydria is conductive to a copious growth of aerobic bacteria in the duodenum, and this abnormal flora contains forms representative both of the mouth and of the lower levels of the digestive tube.

EPIDEMIC ENCEPHALITIS IN FOXES. R. G. GREEN, N. R. ZIEGLAR, H. O. HALVORSON, B. B. GREEN and E. T. DEWEY. (From the Department of Bacteriology, University of Minnesota, Minneapolis, Minn.

During the past three years an exhaustive study has been made of a disease in epidemic form occurring on silver fox farms. Deaths in a single epidemic have totaled more than 700. The disease is characterized typically by weakness, convulsions and a lethargic state. The onset is usually sudden, the animal dying in from one to three days after the onset. Gross pathologic changes are not marked, consisting mainly of hemorrhages in various organs, including the brain and the spinal cord. Microscopic pathologic changes of the brain and spinal cord show abnormal collections of cells, more frequently about the blood vessels; hemorrhages into the surrounding tissues are common. The disease has been transmitted consistently by the injection of the brain and spinal cord taken from a sick animal into normal foxes by cisterna puncture or intracranial injection. Whereas the mortality of the natural disease is from 10 to 25 per cent of animals on a ranch, the mortality in artificially infected animals is close to 100 per cent. The exact nature of the infective agent is as yet undetermined, although a streptococcus is under suspicion. The virus appears to be neutralized by castor oil soap. Animals vaccinated by means of a soap virus mixture appear to have resistance to artificial infection.

SYMPTOMS OF EPIDEMIC ENCEPHALITIS OF FOXES. R. G. GREEN. (From the Department of Bacteriology, University of Minnesota, Minneapolis, Minn.)

A portion of the moving picture records of both ranch animals and experimental animals used in the study of encephalitis of foxes is given.

HEMORRHAGIC SEPTICEMIA OF FISH. DAVID L. BELDING. (From the Boston University School of Medicine, Boston.)

Fish septicemia, a disease of considerable economic importance to fish culturists in the New England and Middle Atlantic States, is reported in several Massachusetts hatcheries. The causative organism is a member of the *Pasteurella* group apparently identical with *B. salmonicida,* first described in Bavaria by Emmerich and Weibel. Several strains have been isolated from hatchery and wild fish. The disease seems specific for fish, since attempts to inoculate other poikilothermal animals have proved unsuccessful. No species of salt or fresh water fish common to New England waters is immune. Infection is transmitted by contact, contaminated water and ingestion.

The type of disease is determined by the rapidity of death. The epidemic form is characterized by a septicemia without local lesions, and nonepidemic form by necrotic areas in the muscles and subcutaneous tissue. No satisfactory prophylactic treatment has been discovered. Certain epidemics have been held in control by keeping the water below 55 F.

A PLEOMORPHIC ANAEROBE: THE ETIOLOGICAL ORGANISM IN A FATAL MENINGITIS. EDNA G. JACKSON. (From the Henry Ford Hospital, Detroit.)

A markedly pleomorphic, anaerobic, gram-negative bacillus is described which was isolated from a fatal case of meningitis. The organism was obtained from cultures of the spinal fluid, and also from blood cultures taken before

death and at autopsy. It is virulent for laboratory animals, and this virulence has been retained after several months' growth on artificial mediums. The cultural characteristics are described, and also the results of animal inoculation.

COLLOID CHEMICAL ASPECTS OF THE KAHN REACTION. R. L. KAHN. (From the Michigan Department of Health, Lansing, Mich.)

The correlation of the author's observations on the precipitation phenomenon with syphilitic serum especially with reference to the Kahn reaction, with factors which govern other colloidal precipitation reactions.

PRINCIPLES OF ANTIGEN CORRECTION FOR KAHN REACTION. R. L. KAHN, ELIZABETH MCDERMOTT and GRACE LUBIN. (From the Michigan Department of Health, Lansing, Mich.)

Over four years ago, an antigen having a certain degree of sensitiveness with syphilitic serum was selected on the basis of clinical serologic studies, as standard for the routine Kahn test. All antigens prepared since then have been made to conform to this standard. Antigens prepared from different lots of heart muscle according to the prescribed method, may have a degree of sensitiveness greater or less than the standard. The sensitiveness of a given antigen at its titer is closely related to its lipoid content. Both dilution and concentration of an antigen when continued to excess, will ultimately decrease its sensitiveness with serum, maximum sensitiveness for any antigen being associated with optimum lipoid content. Thus, if the lipoid concentration of an antigen at its maximum sensitiveness is increased or decreased 25, 50, 75 and 100 per cent, it will be found that the greater the change in concentration in either direction, the greater the reduction in sensitiveness. These facts form the basis for antigen correction.

If an antigen is less sensitive than standard requirements, presumably it is either too rich or too poor in lipoids. If too rich, it is diluted with cholesterolized alcohol; if too poor — and this can be readily recognized from its behavior with salt solution — it is concentrated by the addition of lipoids. The increase or decrease in concentration required to bring such an antigen to standard sensitiveness can be determined by making Kahn tests with syphilitic and nonsyphilitic serum, using standard antigen as a control. If a new antigen is more sensitive than standard requirements, its sensitiveness may be reduced by increasing or by decreasing its concentration. Since reducing the concentration of the antigen by diluting with alcohol is technically simpler than concentrating it, the former method is usually used. After correction, an antigen does not require retitration but may be used in a titer of 1 cc. antigen + 1.1 cc. saline.

It should be emphasized that an antigen may be reduced to dryness by evaporation and the residue taken up in a volume of alcohol corresponding to that of the original antigen, without decreasing the sensitiveness.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Jan. 12, 1928

EUGENE L. OPIE, *Presiding*

LINITIS PLASTICA WITH POLYPOSIS AND ADENOCARCINOMA. E. L. ELIASON.

A man, aged 45, was admitted to the University Hospital for surgical treatment, being referred by Dr. T. G. Miller of the gastro-enterological clinic.

The chief complaint on admission was vomiting and epigastric fulness. The patient was well until six weeks before admission, when a sense of fulness in

the epigastrium and nausea and vomiting developed, occurring three or four hours after each meal. Blood was not present in the vomitus. During his illness, the patient had lost 20 pounds (9 Kg.) in weight. On physical examination, the abdomen was not tender or rigid. A sausage-shaped mass was palpable in the epigastrium. This mass was fixed but not tender. Roentgen-ray examination revealed pyloric obstruction, probably due to neoplasm, duodenal defect and complete retention of six hours' duration.

On Oct. 26, 1927, the patient was operated on, and the pyloric end of the stomach showed a hard, indurated mass involving the entire wall and extending toward the cardiac end of the stomach for a distance of about 3 to 4 inches (7.6 to 10.1 cm.). This was indurated, edematous, smooth and inflexible. It involved the entire circumference of the viscus and ended abruptly at the pylorus below and at Hartmann's line above. Involvement of the lymph node was not demonstrable. Extending through the pylorus was a palpable nodule. The mass was excised by a subtotal gastrectomy, and a Polya anastomosis was made.

The pathologic report follows: the wall of the stomach was thickened throughout with a polyp extending through the pylorus. There was a small intramural abscess at the base of the polyp. Microscopic examination revealed a chronic inflammatory process in the wall of the stomach and an adenocarcinoma of the polyp.

MALIGNANT PAPILLOMA OF THE STOMACH. E. L. ELIASON.

A woman, aged 61, was admitted to the University Hospital on Oct. 24, 1927, for surgical treatment, being referred by Dr. T. G. Miller of the gastroenterological clinic.

The chief complaint on admission was of diarrhea for the past six years. In view of the subsequent observations, it is interesting to note that the patient had never had symptoms referable to the stomach. The diarrhea had increased during the last three months, and the patient had lost 35 pounds in weight (15.9 Kg.) during the last six months. Masses were not palpable in the abdomen on physical examination. The red cell count was 4,280,000, and the hemoglobin content was 63 per cent. Free hydrochloric acid was not found on gastric analysis. Occult blood was demonstrated both in the gastric contents and in the stool. The Wassermann reaction and the results of urinalysis were negative. Roentgen-ray examination revealed probable carcinoma of the stomach involving the greater curvature. The colon and the small intestine were normal.

The patient was operated on Nov. 30, 1927. At the junction of the middle and lower third of the stomach, a soft, doughy mass could be palpated; this did not appear to involve all coats of the stomach, as the wall of the stomach could be rolled over the mass. The stomach was opened, and three soft, pedunculated masses ranging from the size of an olive to that of a small lemon could be picked up and drawn out. One of these showed a hemorrhagic, ulcerated area. The diagnosis was multiple papillomas. A sleeve resection of the stomach was performed, about a third of the stomach including the masses, being excised. The gallbladder, liver and duodenum were normal.

Gross pathologic examination showed three soft, friable, pedunculated tumors arising from the mucosa of the stomach. The diagnosis of these tumors by microscopic examination was "benign tumors, papilloma, with malignant change in one of them."

PRIMARY CARCINOMA OF THE LIVER. GEORGE M. ROBSON.

A colored man, aged 46, was admitted to the University Hospital complaining of abdominal pain, jaundice and loss in weight. Except for hemorrhoids, he had been well until three months previous to admission, at which time he consulted a physician because of hemorrhoids and jaundice. From this time

he suffered from jaundice, progressive weakness, loss in weight and abdominal pain. In the University Hospital, a large, nodular liver, deep jaundice and ascites were noted. He died suddenly from intra-abdominal hemorrhage.

A massive intraperitoneal hemorrhage, apparently from the rupture of one of the portal vessels, all of which were greatly dilated, was the immediate cause of death.

The liver was huge, weighing 5,300 Gm. Its entire surface was roughly nodular and deeply bile-stained. The nodules varied from a few millimeters to a few centimeters in diameter. Many of the nodules were soft and orange-yellow. Others were firm and reddish brown. The cut surface showed the picture of an advanced cirrhosis of the perilobular type studded with soft, yellowish tumor nodules of various sizes. The main portal vein and its branches were filled by large, friable masses of tumor tissue, and many small veins were plugged with the same material. There were numerous secondary nodules in the gallbladder and a few small ones in the lungs.

Microscopic examinations revealed marked cirrhosis of the perilobular type with dense bands of fibrous connective tissue separating the liver tissue and tumor into nodules. Many veins were plugged by the tumor tissue. One section showed the wall of a fairly large vein penetrated by the tumor which streamed through a narrow opening to form a large nodule in its lumen. A section of the mass from the portal vein showed it to be made up of a fairly well preserved tumor without any thrombus formation.

The general structure of the tumor was markedly uniform. It was made up of villous or cordlike cellular masses seen cut either transversely or longitudinally. These cell masses were separated by wide capillary spaces, but no stroma extended between the cells. The cells were usually large polyhedral ones with an abundant granular cytoplasm and large slightly irregular or rounded nuclei. The nuclei were vesicular, with loosely arranged chromatin. Between these cells, rounded plugs of bile were seen. The central portions of the cellular cords were often degenerated or necrotic.

Emboli of tumor cells were seen in the lungs, suprarenal, pancreas, and a mesenteric lymph node. Small secondary tumors of identical structure were seen in the gallbladder and lungs.

In this tumor, the apparent ability of the tumor cells to secrete bile indicates its origin from liver cells. Its diffuse distribution in the liver suggests that it was of multiple origin, although, in view of the extensive invasion of the veins, this could also be accounted for by metastasis. At least it seems clear that this was a primary malignant tumor arising from liver cells and associated with an advanced cirrhosis. This is a well recognized type of primary tumor of the liver — the carcinomatous cirrhosis, or carcinoma with cirrhosis of Hanot and Gilbert.

GANGRENE OF THE URINARY BLADDER. HOWARD R. HANSELL.

The specimen is the bladder of a white man, aged 32, who was admitted to medical service "B" at the Episcopal Hospital in September, 1927 with pneumonia of the lower lobe of the right lung. Throughout the patient's illness, which lasted for nineteen days, distention of the abdomen was a marked feature; for this, the patient was given numerous turpentine stupes and two turpentine enemas. A pseudocrisis occurred on the fourth day, and it was found that the bladder was greatly distended. A catheter was inserted, which, instead of the usual method of sterilization, had been passed through a weak mercuric chloride solution and then rinsed in water. Forty ounces of urine were obtained. The patient had to be catheterized subsequently three times, the catheter being sterilized by the usual method each time. He continued to look toxic, and began to complain of burning on urination. The urine was alkaline in reaction and grossly bloody. This condition continued until the time of his death, which occurred nineteen days after admission.

Examination at autopsy showed congestion of the lower lobe of the left lung; unresolved pneumonia of the lower lobe of the right lung and a small area at the apex which had recently been affected. The bladder contained 250 cc. of a greenish-yellow mucopurulent fluid.

A cast of the entire mucosa of the bladder was found attached to the wall of the bladder in a few small areas. When this was easily stripped off, a purplish-green irregular necrotic surface was seen. The wall was thickened throughout.

EXPERIMENTAL STUDY OF CASES OF LEUKEMIA. EUGENE L. OPIE.

The literature on leukemia and aleukemic lymphoma has been reviewed to determine how the disease may be studied to the best advantage by experimental methods. None of these diseases can be transferred from one species to another. There is no evidence that leukemia of mammals can be transferred to other animals of the same species, and the same statement can be made of aleukemic lymphoma.

One type of tumor which has its origin in the lymph nodes of dogs is readily transmitted by natural and artificial means, but this so-called infectious lymphosarcoma of the dog has many characters which distinguish it from the neoplasms.

The disease known as leukemia of fowls is easily transmitted to other fowls and, in the opinion of most who have studied it, is caused by a filtrable virus.

One investigator attempted to transfer leukemia from one human being to another, but failed. Numerous attempts to transfer leukemia from man to lower animals have been unsuccessful.

Much of the literature concerning leukemia and related diseases in mammals is untrustworthy; nevertheless, it is evident that cases of leukemia conforming with the types found in man occur in many if not in all domestic animals and in small animals available for experimental studies. Aleukemic lymphomatosis apparently occurs much more frequently. Lymphatic and myelogenous leukemia, aleukemic lymphoma, lymphosarcoma and perhaps Hodgkin's disease occur in mice. Opportunity for the experimental study of cases of leukemia resembling the condition in man is not lacking, but experiments have as yet been unfruitful.

The transmissible tumor of dogs, known as infectious lymphosarcoma, has external characteristics which are similar to those of lymphosarcoma, but the origin of cells which form the tumor is uncertain, and it has not been shown that they are lymphocytes or are derived from lymphocytes. Such growths have little resemblance to tissue newly formed as the result of inflammation. Transmission from one animal to another is like the transmission of a contagious disease, but no micro-organism has been found in association with these growths. Resistance which appears in animals with the tumor has some resemblance to that caused by bacterial infection. One group of observers maintain that transplanted tumor cells undergo necrosis, and that the new tumor is derived from cells of the host. Another group hold the opinion that the tumor is formed by multiplication of transplanted tumor cells. The nature of the disease is still uncertain.

Diseases which closely resemble leukemia of man occur in fowls. The changes in the blood and in internal organs are similar though not identical, differences being explainable by wide differences between the two types of animals. Transitions from lymphomatosis to a disease with much resemblance to myelogenous leukemia, on the one hand, and to anemia with hyperplasia of precursors of erythrocytes on the other, are more conspicuous than in man. The recorded evidence indicates that these various changes affecting the blood and blood-forming organs are transmitted by a single virus which is ultramicroscopic and filtrable by the methods usually employed. In this respect they differ from mammalian leukemias and resemble certain malignant tumors of fowls (Rous sarcoma).

NEW YORK PATHOLOGICAL SOCIETY

Anniversary Meeting, Jan. 12, 1928

DAVID MARINE, *President, in the Chair*

MULTIPLE PERITONEAL CYSTS AND THEIR HISTOGENESIS. ALFRED PLAUT.

The inner genital organs and the appendix were removed from an unmarried woman, aged 44. The clinical and anatomic diagnosis was myomas uteri. The tubes, ovaries and appendix were normal. In addition to these organs, several extremely thin-walled, white, flabby cysts were sent to the pathologic department. They had been loose in the peritoneal cavity, and their removal had not caused any difficulty for the surgeon. There was no history of previous abdominal disease. The fluid in the cysts was like water; it contained some sodium chloride, but neither albumin nor reducing substances (Benedict test) were present. Cells were not found in the sediment. The cysts varied in size from that of a large walnut to that of a banana. Some of them were ovoid, but most of them were irregularly sausage-shaped, with distinct constrictions. The walls looked like fine tissue paper; except for a few small thickenings, they did not show any detail of structure to the naked eye.

Microscopically, the wall of the cysts showed several layers of connective tissue, partly straight, partly wavy; they all were homogeneously red in the van Gieson mixture; muscle fibers and elastic tissue were not found. There were few blood vessels in which the endothelium was normal. At some points, an extremely thin layer of connective tissue formed the wall, together with a single layer of flat, lining cells. The inner lining of the cysts consisted of one or several layers of cells; in most instances, seemingly piled up cells may be cut tangentially and belong to the same one or two layers. But there were doubtless straight cross-sections in which from four to five layers of cells could be seen. Many cells were flat and long tailed, with the axis parallel to the wall, with an ovoid, clear nucleus and several distinct, small nucleoli. Others were similar in size and shape, but their nuclei were pyknotic. Some cells, protruding into the lumen, appeared as cuboidal, even as cylindrical elements, with the axis and that of their nuclei at a right angle to the cyst wall. In many of these, the free margin of the cytoplasm, sometimes rather conspicuous, was indistinct and ragged; at some spots it was suggestive of plasmatic protrusions, perhaps of cilia (Henriette Karas: *Virchows Arch. f. path. Anat.* **188**:138, 1907). At several points, mostly in oblique sections of the wall, clear spaces could be seen between the cells and the typical intercellular bridges. The picture reminded one immediately of skin epithelium from the middle layers of the rete malpighii. Intercellular fibrils could not be seen, and Ranvier's nodules were not evident. When these observations are taken into consideration, how shall the cysts be named? The actively growing tissue, the lining cells namely, were epithelial; the correct morphologic nomenclature would be benign cystic serosa-epithelioma. The term serosa-epithelioma has been proposed by Herzog. It is based on the opinion that the lining cells of the peritoneum (and of other serous cavities) are to be named epithelial cells. At present, however, opinions vary as to how to define epithelium, endothelium and connective tissue; how far to attempt to draw rigid borderlines, and how far to admit transitions between these different classes of cells. The trend is more and more to think of the serosa cells as epithelium, and our observation of the intercellular fibrils in a peritoneal tumor might be considered one step more in this direction. In the long and intense discussions concerning the origin of peritoneal tumors, the presence or absence of intercellular fibers has not been used as an argument. How far it can be used as such depends on the interpretation.

Epithelial fibers as found in the cysts examined, closely imitating the well known picture from the skin and demonstrable in the routine slide stained with

hematoxylin and eosin, will probably be considered a sign of epithelial character, strictly speaking. The interpretation is more open to discussion when the bridges between the cells are less regular and more difficult to demonstrate. In 1893, Kolossow claimed that all lining cells have such bridges, and he wanted even the vascular endothelium called epithelium; however he has not had many followers. In 1905, Krompecher identified the plasmatic cell connections in some kinds of epithelium (reticular epithelium) with the fibrils of collagenous tissue. Admitting that the specificity of tissues is not absolute, one must try, nevertheless, to keep the different classes of cells apart in one's mind and in the nomenclature; otherwise there will be chaos. The seeming transitions between epithelium and cartilage in certain tumors of the parotid gland, or the once reported high, mucus-producing epithelium on a heart valve cannot induce one to consider the involved tissues as closely related to each other. Peritoneal lining cells, however, assume the character of epithelium, *sensu strictiori,* so frequently that a close relationship is obvious. While in the older literature (Marchand), the changes due to inflammation have been discussed freely, noninflammatory overgrowth of peritoneal cells has recently given still more impressive pictures. Downgrowth of peritoneal surface cells forms real glands which look exactly like an endometrial gland. In the female pelvic organs, one finds them in an astonishingly large percentage of cases. When hemorrhage or remnants of hemorrhage are seen in the pelvis, one can be pretty sure to find glandular structures springing from the peritoneum of the tube, broad ligament or uterus. In tubal gestation, it seems to be nearly the rule. When one compares the rare instances of high epithelium and gland-like structures springing from definite vascular endothelium, one cannot help putting the peritoneal (and pleural) cells much nearer to the true epithelium than the lining cells of blood vessels and lymph vessels. They also spring from the mesoderm directly from which undoubtedly epithelial structures like the tubules of the kidney are derived, while the endothelium of the blood vessels originates from the mesenchymal wandering cells which do not give origin to any truly epithelial tissue. Furthermore, the peritoneal cells are lining cells from the beginning (Waldeyer, Ribbert, Maximow). The only occurrence which is not exceptional, as far as my knowledge goes, it in lymph nodes in or near the pelvis. This is the most frequent location of high epithelial cells in the peritoneum and also reminds one of Marchand's statement that different parts of the celomic epithelium might behave differently. Serosal cysts are frequent on the posterior surface of the tube, but rare on the anterior. Applying these histologic considerations to the peritoneal cysts, it seems not to be expedient to call them endothelioma. The name endothelioma of peritoneum has been applied rather loosely. When it is shown convincingly that a tumor originated from the lymph vessels under the peritoneal covering, the name will apply. The decision whether the lining cells of the serosa are the source of the tumor or the lymph endothelium under it might be extremely difficult or even impossible in the single case. The chemical examination of the fluid of the cyst cannot decide this question. For the reasons mentioned, I call the tumor in my case benign cystic serosa-epithelioma of the peritoneum.

Reports of cases in which identical or similar tumors occurred are scattered in the literature; most of them have been published by surgeons. Cysts, cystoma, cystadenoma, lymphangioma and lymphangio-endothelioma are the most frequently used names. In some cases, the cystic masses filled the entire abdomen and contained several gallons of fluid; the enormous distention of the abdomen formed a peculiar contrast with the lack of any severe general symptoms. In one patient, the removed fluid weighed more than the patient himself. All parts of the peritoneum have been found as the seat of the cysts, the omentum majus being the site of preference. The disease is more frequent in children and in young persons, but it has been found accidentally in old people at autopsy. The majority of cases (perhaps from 70 to 75 per cent) occur in

women. The condition may be congenital. Sometimes new cysts form after operation. Some patients apparently are cured. In the patient whose case I report signs of recurrence could not be detected nearly two years after operation. In one well observed case (Borst: Geschwuelste, vol. 1, p. 320) a multiple cystic tumor of the peritoneum was found, together with a diffuse, polymorphous, partly cancer-like "endothelioma" of the peritoneum. This coincidence of the two rare tumors probably is not merely accidental.

DISCUSSION

ALWIN PAPPENHEIMER: About two weeks ago, I performed an autopsy on a woman who died of carcinoma of the esophagus; a cyst about the size of a small egg was situated in the retroperitoneal areolar tissue mesial to the cecum. It had an extremely delicate wall and was apparently multilocular, although this was hard to determine because the cyst collapsed when it was removed. It was lined with flattened endothelial-like cells. I interpreted it as either a lymphangiectasis or possibly a lymphangioma. It did not seem to me in this case that there was any indication of epithelial origin, but perhaps I was dealing with a different type of structure.

MAX GOLDZIEHER: I have recently seen two tumors which may fall in this group. One tumor was from a middle-aged woman whose entire abdomen was full of cysts, and the only difference in them macroscopically was that some of them were pinkish. They were unilocular, pedunculated, or deeply embedded in the omentum, in the mesentery and in the other subperitoneal structures. Some were free in the peritoneal cavity. In the same case, there were small cysts of the ovary. Microscopically, the picture was similar to that described by Dr. Plaut. Nevertheless, I thought of the possibility that some of the small ovarian cysts might have ruptured and their epithelium might have been implanted on the peritoneum; accordingly, I interpreted the case as one of multiple implantation metastasis of ovarian epithelium. I was at a loss to explain the other tumor. It was a single cyst on the left side embedded in the retroperitoneal fatty tissue. The cyst was about the size of two fists, and its epithelium was like that described by Dr. Plaut, with the exception of small areas in which it was high, cylindrical and showed goblet cells. The contents of the cyst showed traces of mucus. I thought of some embryologic displacement of intestinal epithelium. I do not claim that that interpretation is right, but I do not think one can prove any other origin of these cysts.

ALFRED PLAUT: In regard to Dr. Goldzieher's first case, I wonder whether implantation from an ovarian cyst would show such flat cells. Implantations from ovarian cysts which I know of generally either are of the pseudomucinous type or have cuboidal epithelium throughout. Certainly secondary stretching and filling of the cyst might make the cells flat, but I wonder if it would make them universally flat, and make the cyst as thin-walled as it is here. I cannot deny the possibility, but it does not seem probable to me.

Many of the cells in the case presented coincide with the description given by Ewing and others as typical of endothelial cells: pavement-like cells, with large clear vesicular nucleus and with many distinct nucleoli. Heidenhain's stain especially brings that out. But side by side with these cells there are others which resemble skin epithelium. There are cuboidal and cylindrical cells. I wonder whether the findings of such typical endothelial cells can be taken as a definite indication that the tissue is endothelial.

BACTERIOPHAGE AS A FILTRABLE VIRUS. J. BRONFENBRENNER.

According to d'Herelle's conception, the active agent of transmissible lysis of bacteria (bacteriophage) is an ultramicroscopic virus. The particles of this virus are endowed with all the essential characteristics of living organisms. It assimilates bacteria or their products. It multiplies and forms colonies

(plaques) on solid mediums seeded with susceptible bacteria. It is susceptible to the action of protoplasmic poisons, and is capable of developing a relative degree of resistance to them. Its action on bacteria is analogous to acute infection in higher animals. The corpuscles of the virus enter the bacterial cells by puncturing their membrane, and multiply within the cells, causing them to swell and finally burst. At this time, young parasites are set free and are ready to invade other bacteria. A certain number of bacteria recover from this infection and develop specific active immunity to the virus.

While the majority of observations of d'Herelle have been confirmed repeatedly, a wide divergence of opinion exists concerning the interpretation of these observations. Without denying the abstract possibility of the existence of viruses as primitive forms of life, representing the transition from unorganized to organized matter, a number of investigators believe that bacteriophage does not exemplify such a transition. Thus, the experimental evidence has shown that the particulate distribution of the agent is only apparent and is due to its ready absorption on the surface of colloidal particles of the medium. The size of the particles which are thus apparently endowed with the activity is not uniform and can be varied experimentally by causing redistribution of the agent on the surface of more highly dispersed colloids. The agent does not respire. While it undoubtedly accumulates in the medium in the presence of growing susceptible bacteria, evidence of its actual growth and assimilation of the substratum by it is not present. When an active agent is introduced in a culture of susceptible bacteria, it begins to accumulate there prior to and independently of the lysis of bacteria. When the concentration of the agent in the solution reaches a sufficiently high level, bacteria begin to swell. Measurements of the viscosity of the culture indicate that at the height of the swelling the bacterial mass may occupy twelve or more times its original volume. Cinematographic records show that at the height of swelling bacteria burst without leaving any visible debris in the majority of instances. The ready solubility of the bacterial residue indicates that the cytoplasm must have undergone intracellular digestion during the process of swelling. Chemical analysis of lysed cultures shows evidence of such digestion. These observations suggest that the agent of transmissible lysis of bacteria is not a living virus. It is probably a diffusible metabolic product of bacteria secreted by them during the logarithmic period of growth. This product is toxic to homologous bacteria and is capable of stimulating their metabolic activity. As a result, some of the intracellular material is digested, and the osmotic pressure within the cells is accordingly increased. This is followed by the intake of water. Bacteria swell up to the limit of elasticity of the ectoplasmic layer and burst, setting free the predigested cytoplasm. Somewhat analogous changes have been observed also in the tissue cells of higher animals, following the introduction of certain filterable viruses.

DISCUSSION

ALFRED PLAUT: I would like to know about the resistance of bacteriophage to physical and chemical agents compared with the resistance of bacteria.

J. BRONFENBRENNER: The bacteriophage is more resistant than bacteria. D'Herelle originally stated that in relation to various injurious agents it occupies a position between bacteria and bacterial spores. In a good many instances, this has been borne out by experiments. In some instances, it has not. The resistance of bacteriophage to various injurious agents has been claimed by D'Herelle as one of the evidences of its animate or organized nature. He stresses particularly the lack of resistance to alcohol, which is analogous to that of bacteria. I investigated that carefully, and find that the destruction of bacteriophage by alcohol is entirely related to the coagulation of the carrier or the vehicle protein and not to the phage itself. If coagulation of the protein which carries the bacteriophage is increased by addition

of salts, for instance, the destruction of the bacteriophage is greatly increased. If the protein is eliminated from the culture, one can obtain bacteriophage which resists 95 per cent alcohol for weeks. I think before the question can be answered, in general, it would be necessary to repeat the experiments with various agents like mercuric chloride, phenol and others, to determine what happens, but at least in the case of alcohol it was found that the injurious effect is not due to the effect of alcohol directly on the bacteriophage but to the denaturing effect on the protein vehicle.

JULIUS KLOSTERMAN: Has there been any recent authentic literature on the development of antibodies against bacteriophages? Is it definitely established that one does find antibacterial antibodies as such?

J. BRONFENBRENNER: Yes, that is one of the debatable points to those who think of the bacteriophage as a chemical substance; because if it is a product of bacteria, would it produce autonomous antibodies distinct from antibacterial antibodies? It has been found that different bacteriophages represent entirely separate and distinct antigens. An antiserum prepared against one bacteriophage does not neutralize another bacteriophage, and there might be several bacteriophages which are similar to one another in respect to the extent of their activity for different bacterial species, and yet each may represent a separate antigenic entity. In this respect, the living nature and individuality of the phage as a parasite would perhaps be a simpler assumption to make than to ascribe it to a chemical product of bacterial metabolism. This is not the only difficulty. There are others in the problem, but that is due to the fact that we do not know everything about it. It is a fact that when an animal is immunized with a filtrate of bacteria which have undergone lysis, a specific antibody is obtained which is capable of neutralizing bacteriophage independent of its antibacterial properties.

Book Reviews

L'ANGINE DE POITRINE ET L'ANGINE ABDOMINALE. By D. DANIÉLOPOLU, professor de clinique médicale à la Faculté de médecine de Bucarest, Directeur de L'Institut clinico-médical B de L'Hôpital Filantropia. Price, 140 francs. Pp. 442, with 159 figures. Paris: Masson & Cie, 1927.

This volume presents a fairly full exposition of the present knowledge in regard to angina pectoris. There is a great deal of material which has not been previously collected, but which has been available only in separate and scattered articles. The author states his theory concerning the causative factors underlying the symptom complex, with the supporting evidence, and outlines a surgical treatment based on this foundation.

Angina pectoris is divided into angina pectoris and abdominal angina. Angina pectoris is further divided into the genuine angina and angina with complications. The former is divided into an organic and a nonorganic form. Under the organic form is classified the ordinary case of angina, in which definite changes in the heart or aorta are assumed to be the underlying factor. Under nonorganic angina pectoris are included the cases which are on an apparently neurogenic basis. It is stated that while it is difficult to define the limits of such a group, or to deny the presence of some organic lesions, a few cases must fall into such a classification.

Under angina pectoris with complications is included cases in which anginal pain is associated with dyspnea, or with acute edema of the lungs. It would seem that this grouping would tend toward confusion and not to definiteness of diagnosis. Such cases are associated with definite and usually ascertainable pathologic changes, and should be grouped accordingly.

The term abdominal angina, which includes cases in which the pain is referred to the abdomen, also seems not to tend to clarity.

A quite complete clinical picture is given of angina pectoris, its symptoms and the associated phenomena. Under the latter are included his own investigations with the plethysmograph, showing an increased vasomotor response in anginous patients.

In considering the pathogenesis, the author gives first a detailed and anatomic account of the nerve supply to and from the heart and its vessels, and the physiology of both pathways. This is followed by an account of the blood supply to the heart and its vessels, with physiology, and the pathologic changes found in anginous patients. Based on these completely formulated premises, he advances his own theory of myocardial fatigue and a pressor reflex as the causative factor of angina pectoris.

Myocardial fatigue, as in fatigue of voluntary muscle; results from a loss of balance between the work of the heart, and its blood supply at the moment. As causative factors resulting in a blood supply insufficient for the needs he would predicate atheroma of the coronaries to be predisposing, and the determining factors to be the increased work of the heart and any influence which would diminish the blood flow to the heart muscle, as a coronary vasoconstriction. The resulting deficient blood supply permits the accumulation of fatigue products, which, when they reach a certain threshhold, stimulate sensory nerves, which ultimately cause pain, but have also as an immediate result a reflex pressor action, resulting, among other things, in a further vasoconstriction. Thus is established a vicious circle, with increasing sensory stimulation resulting in pain. If this reflex pathway could be interrupted surgically, without interfering with normal physiologic function, relief could be expected. Based on the evidence afforded by his own work and that of others on the anatomy and physiology of these nerve pathways, and guided

by the results of other operative work in the same field, the author differentiates the pathways which cannot be interrupted without untoward results, and describes his own method of operation.

The operation is performed in two stages. At the first operation the sympathetic trunk is cut above the inferior cervical ganglion, the vertebral, the filaments descending parallel to the sympathetic trunk, and the rami communicantes connecting the inferior cervical ganglion and the first thoracic to the sixth, seventh, and eighth pairs of cervical nerves, and the first dorsal. This operation may be of itself sufficient, at least for a time, and in any case affords enough relief to permit of amelioration before the second operation

At the second operation the trunk of the cervical sympathetic is resected above the inferior cervical ganglion, with any of the descending filaments remaining. The vagus and laryngeal nerves are avoided.

Histories are given of thirteen patients operated on by this method, with almost uniformly good results, and no mortality.

From whatever aspect the volume is considered, clinical, anatomic, physiologic or pathologic, it is of outstanding value to those interested in angina pectoris. Especially does it represent an attempt to approach the surgical problem by those avenues only through which it should be approached.

The book is furnished with adequate illustrations and has a complete index to the literature. An English translation is greatly to be desired. Volumes of such value emphasize the importance of a real working knowledge of French and German to medical students in this country.

STANDARD METHODS OF THE DIVISION OF LABORATORIES AND RESEARCH OF THE NEW YORK STATE DEPARTMENT OF HEALTH. General Laboratory Procedures and the Methods Used in the Department for the Preparation of Media and Glassware, the Laboratories for Sanitary and Analytical Chemistry, the Research, Publications, and Library Department, the Antitoxin, Serum, and Vaccine Laboratories, the Diagnostic Laboratories, the Executive Offices. Augustus B. Wadsworth, M.D., Director. Price, $7.50. Pp. 646, with 70 illustrations. Baltimore: Williams & Wilkins Company, 1927.

This volume is the culmination of some ten years' work in developing complete, detailed directions for the use of old as well as new members of the staff of one of America's best known and most productive health department laboratories. Its purposes are explicitly set forth in the following words (p. xv): "to keep uniform the established methods; to instruct the new worker and prescribe exact procedures for him and for those who are unable to take independent responsibility; and to serve as a guide to the policy which the trained, responsible worker may follow or depart from as the immediate situation demands." And on these scores the reviewer must compliment the persons who have contributed to make this volume. It will be found eminently useful not only in diagnostic and biologic production laboratories as a supplementary vade mecum, but in teaching laboratories, too, as a convenient reference on methods. And to workers as well as directors of many state or municipal laboratories it will serve best, if it brings home to them the shame and disgrace which they have earned by the careless, indifferent or even disgraceful service they render their communities.

It is almost gratuitous to say for this volume that much of it is important and will be widely useful; much of it is largely of local usefulness only; and a considerable portion will shortly be of historical interest only. The sections on general laboratory procedures, the use and care of experimental animals, the methods used in the diagnostic and analytic laboratories are destined to be valuable for perhaps a decade. The methods used in the antitoxin, serum and vaccine laboratories are a mixture of some that are standard everywhere, some that are of tentative and current usefulness and others that are already in need of replacement. Many workers will welcome the complete description of the complement-fixation tests, because few investigators have studied the details

of technic in these tests more carefully than Miss Gilbert and Dr. Wadsworth. But many will raise their eyebrows over the pages on the preparation of scarlet fever toxin and antitoxin and the use of a single strain of streptococcus (Dochez), and the methods used in preparing and standardizing antipneumococcus serum. In fields in which scholars hold to honest differences of opinion, the value of "standard methods" is questionable. It is well to have the methods used in a laboratory "standardized"; but then this volume should have been published in a loose-leaf form lest it tend to add undesirable inflexibility in practice that should everywhere be dictated by the newer knowledge. It would be unfortunate if the abbreviated title on the cover ("Standard Methods") were to replace the full title of the volume.

CLINICAL PATHOLOGY. By P. N. PANTON, Clinical Pathologist to the London Hospital and Director of the Clinical Laboratories, and J. R. MARRACK, Chemical Pathologist to the London Hospital. Ed. 2. Price, 15 shillings. Pp. 459, with 12 plates (10 colored) and 51 Illustrations in the Text. London: J. & A. Churchill, 1927.

The first edition of this book was written by P. N. Panton and published in 1913. The aim was to describe in a reasonable compass such laboratory methods, chemical, histologic or bacteriologic, as are of practical value in the diagnosis and treatment of disease. In the present edition, J. R. Marrack, as joint author, has completely rewritten the chemical sections, which also have been expanded to a considerable degree, and the other sections have been revised and brought up to date. The book is divided into the following sections: Blood (including diagnostic serum tests), Bacteriology (with vaccines and therapeutic serums), Puncture Fluids (pleural, peritoneal, cerebrospinal, etc.), Urinary System, Alimentary System, Eye and Skin, Respiratory Tract and Histology. The methods selected for presentation are described briefly and the meaning of the results indicated clearly. In some sections, notably those on bacteriology and histology, statements occur that are so brief as to be of little or no value if not misleading. For example (page 207): "The Pasteur method of inoculating animals against anthrax, and human beings against rabies, consists of giving a series of injections of the infecting agent of increasing virulence. Haffkine's anti-cholera vaccine is given on a similar principle." On page 209 we read that persons found to be susceptible to scarlet fever by the Dick test can be immunized "by injections of toxin-antitoxin mixture." The fact is, of course, that in immunizing against scarlet fever increasing doses of the pure toxin are injected. The chapter on tumors covers twenty-two pages, and the best that can be said for it is that it outlines in skeleton form the various groups and varieties of tumors. The use of the words "osteogenous" and "hematogenous" as signifying the origin of certain tumors, in the first case from bone-forming connective tissue and in the second case from blood-forming tissue, is not conducive to clearness. Myeloma is said to arise as multiple confluent soft tumors "within the medulla of the vertebrae and long bones," but that is not the usual distribution of myeloma, the characteristic or chief original sites of which are the ribs and sternum "while the vertebrae, skull, femur, pelvis and humerus are less frequently involved, and in the order named" (Ewing). In spite of such lapses and shortcomings the book will be useful to student and practitioner who must rely for guidance in clinical laboratory work on one book of intermediate size.

HOST-PARASITE RELATIONS BETWEEN MAN AND HIS INTESTINAL PROTOZOA. By ROBERT HEGNER, PH.D., Professor of Protozoology in the School of Hygiene and Public Health of the Johns Hopkins University. Price, $3.50. Pp. 235, with illustrations. New York and London: Century Company, 1927.

The knowledge of the intestinal protozoa in man is still largely in the descriptive stage. Explanations of the underlying causes of the relations between host and parasitic protozoa cannot as yet be attempted successfully.

The problems that especially need investigation are enumerated by Hegner as follows: (1) the viability of trophozoites and cysts outside of the body of the host; (2) methods of transmission; (3) the factors involved in excystation; (4) excystation in the host; (5) localization within the host; (6) factors of the intestinal habitat in relation to trophozoites and cysts; (7) pathogenesis; (8) resistance and susceptibility of the host; (9) acquired immunity of the host; (10) resistance and infectivity of the parasite; (11) acquired resistance and agressivity of the parasite; (12) host-parasite adjustments; (13) therapeutics; (14) host-parasite specificity and (15) prevention and control.

Hegner's book gives a clear, orderly and comprehensive account of the present knowledge of the relations between man and his intestinal protozoa, and it will be of great value to all who are interested in intestinal protozoa, particularly as a guide in research.

REAGENZIEN UND NÄHRBODEN. A COMPILATION OF THE MOST IMPORTANT AND EXPEDIENT DIRECTIONS FOR LABORATORY PRACTICE. By E. BÖHM, M.D., and K. R. DIETRICH, M.D., apothecaries and chemists in Berlin. Cloth. Pp. 375. Price, 18 marks. Berlin: Urban & Schwarzenberg, 1927.

Lists of hundreds of culture mediums and chemical reagents for a wide variety of qualitative and quantitative laboratory work, with terse notes concerning their composition, reaction and use, together with tables of atomic weights, solubilities, equivalents in volume and weight percentages for quantitative determinations of sugar and other purposes afford a great amount of information for quick reference. Necessarily, such a compilation is not suitable for detailed studies. The book is in German; it is arranged with helpful subheads and adequate indexing; it is of good size and form for practical use and is recommended for the laboratory book shelf.

PRAKTIKUM DER KLINISCHEN, CHEMISCHEN, MIKROSKOPISCHEN UND BAKTERIOLOGISCHEN UNTERSUCHUNGSMETHODEN. VON DR. M. KLOPSTOCK und DR. A. KOWARSKI. Fifth edition. Price, 13.50 marks. Pp. 509, with 48 text figures and 25 colored plates. Berlin: Urban & Schwarzenberg, 1927.

This little book, designed as a laboratory guide for practicing physicians, accomplishes its purpose admirably in general. Starting with the technic for obtaining specimens, all essential steps in procedure are logically portrayed; so the ultimate diagnosis is nicely made. Differential diagnostic tables are liberally employed. In the chapter dealing with conditions of the skin, the tuberculin, Schick and Dick tests might be advantageously included. Twenty-five beautifully colored plates at the end of the book would perhaps be more useful if they were inserted at appropriate places in the text.

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